

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

HEARINGS
BEFORE THE
SUBCOMMITTEE ON MONOPOLY
OF THE
SELECT COMMITTEE ON SMALL BUSINESS
UNITED STATES SENATE
NINETIETH CONGRESS
SECOND SESSION
ON
PRESENT STATUS OF COMPETITION IN THE
PHARMACEUTICAL INDUSTRY

PART 9

SEPTEMBER 18, 19, AND 25, 1968



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*Ex officio member.

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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, SEPTEMBER 18, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:35 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Hatfield.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. Our first witness this morning is Dr. Harvey Minchew, Acting Director, Bureau of Medicine, Food and Drug Administration.

Dr. Minchew, we are very pleased to have you here this morning. You may proceed to present your statement as you see fit.

STATEMENT OF DR. B. HARVEY MINCHEW, ACTING DIRECTOR, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. ROBERT S. McCLEERY, ACTING DEPUTY DIRECTOR, BUREAU OF MEDICINE, FDA; HARRY CHADDUCK, DEPUTY DIRECTOR, DIVISION OF MEDICAL ADVERTISING, BUREAU OF MEDICINE, FDA; WILLIAM W. GOODRICH, GENERAL COUNSEL, FDA; MORTON M. SCHNEIDER, ASSISTANT DIRECTOR, OFFICE OF LEGISLATIVE AND GOVERNMENTAL SERVICES, FDA; AND DR. ALAN SMITH, DEPUTY DIRECTOR, DIVISION OF ANTI-INFECTIVE DRUGS, BUREAU OF MEDICINE, FDA

Dr. MINCHEW. Mr. Chairman: I appreciate this opportunity of appearing before you this morning to discuss the marketing approval and the promotion of Vibramycin, Chas. A. Pfizer & Co.'s brand name for doxycycline. For the sake of brevity, with your permission, I will submit for the record a statement of my educational and professional background.

Senator NELSON. It will be printed in the record at this point. (The biographical data follow:)

BIOGRAPHICAL SKETCH OF B. HARVEY MINCHEW, M.D.

Date of Birth: May 1, 1932.

Place of Birth: Waycross, Georgia.

EDUCATIONAL AND PROFESSIONAL EXPERIENCE

A.B.—Emory University 1953.
 M.D.—Emory University School of Medicine 1957.
 Intern—University of Arkansas Medical Center 1957–1958.
 USPHS–CDC–EIS (Epidemic Intelligence Service) Fellowship in the Division of Allergy and Infectious Diseases, Johns Hopkins Hospital 1958–1960.
 Residency in Internal Medicine—University of Washington 1960–1962.
 Private Practitioner, Internal Medicine 1962–1963.
 Medical Officer, Food and Drug Administration, Bureau of Medicine, Division of Antibiotic Drugs June 1963–February 1965.
 Medical Officer, Division of New Drugs, Investigational Drug Branch February 1965–July 1966.
 Deputy to the Assistant for Drug Coordination, Bureau of Medicine, May 1965–July 1966.
 Acting Deputy Director, Bureau of Medicine, July 1966–September 1966.
 Assistant to the Director for Professional Development, September 1966–January 1967.
 Deputy Director, Bureau of Medicine, January 1967–Present.
 Director, Antibiotic Task Force, Bureau of Medicine 1966.
 Clinical Instructor in Medicine, Georgetown University Medical School.
 Physician, Group Health Association, 1964–present.

SOCIETIES

American Association for the Advancement of Science of Washington, D.C.
 Academy of Medicine of Washington, D.C.
 The American Public Health Association, Inc.

Dr. MINCHEW. The application for approval for marketing of Vibramycin (called a form 5 application for antibiotics) was submitted by Chas. Pfizer & Co. on June 22, 1966.

It was reviewed by the Office of New Drugs and by the Division of Antibiotics and Insulin Certification.

The original submission was inadequate and additional data were required. On October 13, 1966, we received further analytical data and on the next day, October 14, additional clinical reports were submitted.

By January 11, 1967, the preclinical studies in pharmacology had been reviewed. Our conclusions were that liver toxicity was shown in the dog, gastrointestinal toxicity was exhibited in the dog and the monkey, and thyroid changes were found in the monkey, the rat, and the dog. Nonetheless, the pharmacologist felt that the animal data did not preclude approval, so long as the package insert described the toxicity noted to alert the physician to the possibility of comparable effects in man in clinical use. A final review in May of a longer rat study confirmed these conclusions.

Senator NELSON. Confirmed what conclusions?

Dr. MINCHEW. The conclusions of the animal toxicity that had been seen on the shorter term studies.

By February 15, 1967, the chemical controls review had been completed. Manufacturing controls were considered adequate.

The medical review was concluded the same day. The evaluation was that the drug was another tetracycline similar in safety and effectiveness to the previously approved tetracyclines. Its distinguishing characteristics were more rapid absorption and a longer half life, permitting the drug to be given once or twice a day (rather than the usual four times), in smaller doses, to achieve similar clinical results as those seen in higher and more frequent doses of the older tetracyclines.

Mr. GORDON. Doctor, you talk about toxicity studies in animals. Do

you do any toxicity studies in humans before a drug is released for general use?

Dr. MINCHEW. Toxicity observations or observations for toxicities in humans would be a routine part of investigational phases of the drug. Even though a similar product in the form of other tetracyclines would have been marketed previously, this being a new molecule, it would technically have a phase I period when it was first introduced into man, so that during the phase I, phase II and phase III studies, observations would be made for human toxicity.

The competitive situation in tetracycline marketing is intense. The company sought to include in the labeling for Vibramycin features that would emphasize its safety and effectiveness in comparison with established products. To do this, Pfizer sought to feature the lower, once-a-day dosage, a broader antibiotic spectrum, and an advantage in not causing tooth discoloration—a side effect particularly important for pediatric age groups.

Senator NELSON. When you are referring to tooth discoloration, are you referring to permanent deposits of color?

Dr. MINCHEW. The teeth that would be discolored, Mr. Chairman, would be dependent upon which teeth were being calcified at the time the drug was administered. If the drug were being administered at a time when permanent teeth were in fact calcifying, then the permanent teeth could be discolored.

Senator NELSON. Permanently?

Dr. MINCHEW. The observations on this are not so sound that one can say unequivocally permanently, but certainly they have persisted for as long as some people have been observed.

Senator NELSON. Is this a very dramatic coloration?

Dr. MINCHEW. Yes, sir; it is. It is a very noticeable cosmetic defect. It is not the same in every person, and probably depends upon how much of the drug is deposited and combined with the calcium as the calcification occurs. It is certainly a noticeable and disadvantageous cosmetic defect.

Senator NELSON. And this is a characteristic of all tetracyclines?

Dr. MINCHEW. Yes, in general that is true. I can't say that unequivocally for each and every molecule of the tetracyclines that are available it has been specifically observed. Our position is that until proven otherwise, any tetracycline is capable of causing tooth discoloration because they all will combine with calcium this way.

Senator NELSON. Are there any preparations of tetracycline that has any noticeably less effect than others?

Dr. MINCHEW. I don't know that any studies have been done in terms of the actual incidence of tooth discoloration with each particular dosage form of tetracycline that would give a sound answer to your question.

Our conclusion was that the antimicrobial spectrum of this drug was very similar to that of the other tetracyclines, that the small differences in antibiotic sensitivity were of no practical significance, that the animal studies should be called to the prescriber's attention, and that the drug had the single advantage of less frequent dosage.

Labeling changes were requested—to delete a sentence implying greater effectiveness against *Staphylococcus aureus*, and to modify a claim for efficacy in treatment of genitourinary infection to state

that "certain strains of *Proteus* and *Pseudomonas* have responded to Vibramycin." A claim for acne was regarded as unacceptable. A cautionary statement against use in pregnancy was needed. Under "Adverse reactions," we recommended that the effects on the nails be added, that the observations in animals of liver and thyroid changes of undetermined significance be included, and that rare adverse effects on blood be reported.

We had discussed some of this tentatively in January, when Pfizer representatives called to inquire about progress on the application, and we met with them again on February 14, 1967, to go over the points I have noted.

The company disagreed strongly with our recommendations that the observations regarding animal thyroid effects should be in the labeling. They felt that this would place them at a competitive disadvantage in relation to other products whose labeling included no such discussion. They also did not want to delete the statement regarding efficacy in the treatment of *Staphylococcus aureus* infections.

Senator NELSON. May I interrupt a moment? The sentence above that, "They felt that this would place them at a competitive disadvantage in relation to other products whose labeling included no such discussion." Are you referring to other tetracyclines?

Dr. MINCHEW. Yes.

Senator NELSON. Did the other tetracycline products indicate the same animal thyroid effects?

Dr. MINCHEW. Yes, sir; in general they do show similar effects in the animals, and the inequity which is described here as having been emphasized by Pfizer is a result of evolutionary changes that are always going on in terms of package inserts.

Senator NELSON. Did you require the other types of tetracycline to refer to the animal thyroid effects?

Dr. MINCHEW. We have not to date, but we are currently actively revising the labeling of all tetracyclines. This was initiated in the spring of 1967.

Senator NELSON. So that all of them will be required to have the same reference to the animal thyroid toxicity?

Dr. MINCHEW. This is our intention; yes, sir.

Senator HATFIELD. What is your intention? How do you implement your intention? I think that the way you describe it, it sounds like there is a certain inequity here that you are imposing upon one company that you are not imposing upon other companies. Why haven't you taken steps already?

Dr. MINCHEW. We have taken steps to discuss with them revisions in the package insert.

Senator HATFIELD. Are they still marketing under the old methods?

Dr. MINCHEW. Yes, sir.

Senator HATFIELD. What is your time factor?

Dr. MINCHEW. The time factor in this one has now been drawn out to over a year now since we began negotiations and discussions with the companies about changing the package inserts of all of the tetracyclines.

Senator HATFIELD. I am not quite certain as to your procedure. It sounds like you are rather negligent in not taking faster action, if you think it is important enough to have it put on Pfizer. Why haven't you taken immediate steps to have it included in the others?

Dr. MINCHEW. We have taken immediate steps in terms of initiating an effort to get this done. At the same time, we could not——

Senator HATFIELD. How long has it taken?

Dr. MINCHEW. This is a highly variable thing. There are several manufacturers of the tetracyclines. We wrote all of the manufacturers, I believe in the spring of 1967 or the winter, I would have to check that date, requested a meeting with them to discuss class labeling of the tetracyclines.

Senator HATFIELD. December 1967.

Dr. MINCHEW. I would have to check the date. It was either in the winter or early spring of 1967.

Senator HATFIELD. You get worse mail delivery and mail service than we do, don't you?

Dr. MINCHEW. I don't know the condition of yours. Ours does have problems.

Senator HATFIELD. You mean you are almost a year involved in this thing?

Dr. MINCHEW. In changing the class labeling of tetracyclines, yes, sir.

Senator HATFIELD. Is this typical of your bureaucracy?

Dr. MINCHEW. I would not say it is typical. It certainly is an example of our efforts to handle a large number of manufacturers with a very complex question of making uniform labeling.

Senator HATFIELD. How much longer do you think it will take?

Dr. MINCHEW. I can't say because it will be dependent upon some degree of concurrence being reached by a variety of people, and I could not honestly give you an estimated date of completion.

Senator HATFIELD. In other words, you want Pfizer under this special regulation that you have not yet implemented on these other pharmaceutical houses.

Dr. MINCHEW. For this particular product, yes, sir. I think, for example——

Senator HATFIELD. But these other products of these other houses have been on the market and are still on the market.

Dr. MINCHEW. And including some of Pfizer's; yes, sir.

Senator HATFIELD. And you claim some of the same factors are involved in their product that should be labeled as you now require Pfizer; is that correct?

Dr. MINCHEW. And I just would like to make a point also——

Senator HATFIELD. And you have been almost a year in not getting this implemented on the other houses; is that correct?

Dr. MINCHEW. And Pfizer; yes, sir.

Senator NELSON. May I ask a question here? Does the Pfizer package insert include this specific reference to animal thyroid effects now?

Dr. MINCHEW. In the Vibramycin. Pfizer has other tetracycline products currently on the market that do not have it, which will have to have it when we are able to implement across-the-board changes.

Senator NELSON. So Pfizer with its other tetracyclines along with all the other companies with their dosage forms, do not now——

Dr. MINCHEW. Have this animal pharmacology section, that is correct.

Senator NELSON. But in this Vibramycin, issue is raised prior to approval of marketing of the drug?

Dr. MINCHEW. That is correct.

Senator NELSON. The dosage form.

Dr. MINCHEW. It is our feeling that when a new product is becoming available, even though it may have factors in common with already marketed products, that we must at the time of approval of this new drug put the very best labeling into effect which we can. In this case, it does create an inequity until the products which are already marketed, including Pfizer's others, can all be put in a similar labeling position.

Senator HATFIELD. Mr. Chairman, I understand that, and I think that is a very proper action that you take on the new products as they come on to the market. What I don't understand is the length of delay that is involved here in bringing up to standard or up to the same requirements all of the existing products of other pharmaceutical houses. That is the point that I am trying to get at here. Why is there this—you wrote letters in December of 1967, and you are still dillydallying around on this. Why haven't they been brought up to standard as to the new product? How much longer is it going to take?

Dr. MINCHEW. The only honest answer which I can give you is the total volume of work which the Bureau handles is such that these delays are sometimes inevitable, particularly in an instance where so many different manufacturers are involved, and it has to be discussed with them.

Senator HATFIELD. Are you telling me that you are inadequately staffed?

Dr. MINCHEW. To handle everything as promptly as we would like to, yes.

Senator HATFIELD. Well, what do you consider a reasonable time to update these other products in line with these new products, the requirements you impose upon the new products? What is a reasonable time? What is your bureaucratic time? Let me ask you that question.

Dr. MINCHEW. I don't understand.

Senator HATFIELD. I can tell you what I think a reasonable time is, but what is your standard?

Dr. MINCHEW. I don't understand the bureaucratic time.

Senator HATFIELD. What is it that you find in your own history and your own practices in the FDA as far as the time required on the normal or on the average on updating the existing products to bring them to standard that you have established under a new product that comes into the field as in this instance?

Dr. MINCHEW. This is a highly variable figure. In instances where a labeling change has a very direct implication to human toxicity or is a direct immediate question of public safety, the time period is extremely short.

Senator HATFIELD. Such as?

Dr. MINCHEW. Such as weeks.

Senator HATFIELD. You can do it in a matter of weeks.

Dr. MINCHEW. Yes.

Senator HATFIELD. So it is just a question of how much data is involved, is that right?

Dr. MINCHEW. Not that and that alone though certainly that is a factor.

Senator HATFIELD. What are you doing in the meantime in this case? For instance, if it has taken you almost a year, then it shows there is not very much danger involved evidently. What are you doing? What is the procedure you are involved in now on this case? Are you reading letters or are you holding conferences or what are you doing?

Dr. MINCHEW. The immediate status of this implementation is something on which I would have to check with the operating unit in the Bureau that is handling it. I don't have that information available at this moment. I don't know just exactly where this negotiation is at this point in time.

Senator HATFIELD. I would be very interested in knowing your procedures, if you can do something in a matter of weeks, and then at other times it takes you months. I would like to know what your bureaucratic procedure is on that.

Dr. MINCHEW. What would be the question to which you would like to have a direct answer?

Senator HATFIELD. I would like to know in changing the labeling of existing products to base it upon a new standard that you prescribe, because of your research and determinations arrived at on a new product, you tell me that if there is a great deal of danger involved that you can get all this change brought about in the matter of a few weeks. Now you tell me that in this particular instance that you have been almost a year. My question is simply why the great difference? What are you doing in your procedures in your department that you have to take almost a year in some instances when you can do the same job in weeks, a matter of weeks, in other instances?

Dr. MINCHEW. We can provide the committee with a chronology of the negotiations.

Senator HATFIELD. I don't want a lot of that chronology. I want to know the procedure. I want to know why it takes you so little time in some instances and so much time in other instances. If it is a matter of staffing, then I want to know that. I think the committee should know that. If it is a matter of just poor procedures, administrative procedures, I would like to know that, too. I don't want a lot of papers showing a chronology. I just want to know the basic procedures and administrative practices in which you are engaged.

It seems to me ridiculous that you have got the ability to perform in a few weeks in some instances and it takes you so long in others. These are where you open yourself to criticism, and rightfully so. These companies have every right to criticize your operation, when you put one company under that kind of inequitable economic situations, as you are attempting to do, Pfizer here in this case, and then in almost a year you can't get other companies updated in their labeling.

As I say, you admit here that you can really handle such cases under a danger factor in a matter of weeks, then you open yourself up to bureaucratic charges, and rightfully so, when it takes you so long to get moving in other instances. That is my point.

Senator NELSON. I assume one of the problems in the time factor is that if it is a serious matter, that it takes priority over any other backlog material you have got; is that correct?

Dr. MINCHEW. That is correct.

Senator HATFIELD. Mr. Chairman, then we ought to deal with the question of staffing. I don't think that is any excuse. I think after all that if they have that kind of a problem, that they ought to come in here with the kind of budget that is going to let them maintain a current workload so they can deal in a reasonable time with all of these companies on all of the products.

Senator NELSON. I wouldn't quarrel with that. I think they have been asking for more staff and desired more staff for a long time, but haven't been able to get it out of the Congress. But in any event, in chloramphenicol, for example, you moved forthwith after the hearings here with a letter to 200,000 doctors, and I assume that is because you put aside anything of lesser importance, lesser priority.

The question that still remains, however, and which bothers me, is once you have decided with Vibramycin that in the labeling that would—when did that drug go on the market by the way?

Dr. MINCHEW. August of 1967 it was approved. Now I could not comment when the industry first got it in interstate commerce.

Senator NELSON. Once you made the decision that it was significant enough to require the package labeling of Vibramycin, I think the question raised by Senator Hatfield raises this point. You had already made that decision. It isn't necessary to carry on a dialog back and forth with the rest of the companies on their labeling. It would seem to me he has made the point that once you have made that decision you ought to order the other companies in their future package labeling to make this amendment without any delay. I think that is a valid point raised. Is there any response you have to that?

Dr. MINCHEW. Yes, sir. The only point I would make here, though I certainly in no way disagree with the desire which you obviously have, is that we have also to be as efficient as is possible and as equitable as possible. The particular labeling changes which we are talking about far exceed just the animal pharmacology section. They did involve other matters which we felt that it was fair and equitable to discuss with the industry in terms of a format for presenting the indications for the drug and this type of thing.

It did involve a lot more variables than just simply establishing the edict that animal pharmacology sections shall be present. We did also discuss some of these with our Medical Advisory Board.

Senator NELSON. The point raised here, if there are competing products, and I agree when a New Drug Application is made and you decide upon the package insert, you use the most up-to-date information you have. You notify the doctor. But it seems to me in any competing product, once you have made that decision, you certainly ought to move as expeditiously as possible in directing an amendment to the package insert of the other products, or it is subject to, I think, a valid complaint.

Dr. MINCHEW. And we agree that the time period is certainly longer than we would prefer. In the interest of giving the doxycycline as equitable a treatment as is possible in this regard, the package insert does state that the animal toxicities which are observed and described in their labeling occur with other tetracyclines.

Senator HATFIELD. May I ask one more question? Could you tell me what your requests were in the budget for additional staff for this year that were denied you, the numbers that were denied you or the dollars that were denied you?

Dr. MINCHEW. Not for the coming year, because we have not received that in final yet.

Senator HATFIELD. Have you made requests for specific additional staff in your division, in the Bureau of Medicine?

Dr. MINCHEW. Yes, sir; we have. We are currently operating under a personnel freeze system, under a replacement system where at the present we can only hire one for every two losses, so that even approved figures at this point in time don't enable us to obtain the staff.

Senator HATFIELD. About how much understaffed do you consider yourself at this point?

Dr. MINCHEW. Well, we are currently right now at around 480 people in the Bureau of Medicine, with an approved number last year of somewhere around 560.

Senator HATFIELD. And you made a request for more in the coming—

Dr. MINCHEW. Yes, sir; we have.

Senator HATFIELD. What figure is that?

Dr. MINCHEW. I would have to check that figure. I can't give it to you right now.

Senator HATFIELD. Thank you.

Dr. MINCHEW. The only other point I would make that I think is critically related to the discussion of this specific drug is that, in this area, and that is the area of physicians with specialty training in infectious diseases and antibiotic therapy, they are even much more scarce, much harder to find than a physician in general.

Senator HATFIELD. When do you expect to have your work completed on the insert label updating of these other products in the industry?

Dr. MINCHEW. I would have to check with the operating division, Senator.

Senator HATFIELD. You don't know?

Dr. MINCHEW. I do not know right at this moment, no.

Senator HATFIELD. Yet you have great detail to give us today on everything that Pfizer did or did not do in this whole case, in this whole controversy, and yet you do not know what this whole time schedule is in your own agency on updating these other insert labels?

Dr. MINCHEW. This is something I would have to check with the operating division. I have these details concerning this particular drug because this was the drug I was asked to comment upon.

Senator NELSON. That may be my fault, Senator. I asked them to discuss detailing and promotion of the drug, and I didn't specifically ask this question, but I assume that you can produce it for the record for us.

Senator HATFIELD. I think it would be very important, Mr. Chairman, to see how the agency is moving on the other pharmaceutical houses on this drug.

Senator NELSON. Please go ahead.

Dr. MINCHEW. A revised "package insert" received March 10, 1967, still did not contain the animal toxicity data, made claims that Vibramycin had a different spectrum than other tetracyclines, did not list all the warnings and adverse reactions recommended, and included some diseases in the indications section for which efficacy had not been shown. Changes we considered necessary in the labeling were further discussed with the company in a telephone conversation on March 30, 1967, and at a meeting on April 19.

Revised labeling submitted May 10 was still considered unsatisfactory. There were further meetings and telephone conversations about the labeling held on June 28, July 7, and July 10.

On July 7, 1967, a representative of Pfizer, called the Commissioner to urge prompt action on the application, stating that everything had been approved and that clearance had been too long delayed. Dr. Goddard had previously invited the industry to bring to his personal attention any instances of what is regarded as undue delay in new drug clearance.

The final clearance was in process during the week of July 24. A monograph establishing standards of identity, strength, quality, purity, and safety, and the final labeling describing safe and effective conditions of use were the last parts of the clearance.

This final review developed the fact that we did not have a firm understanding with Pfizer as to the conditions under which the drug would be introduced and promoted to the profession. While the file indicated that all questions had been resolved, the labeling submitted by the firm did not support this.

Three defects were identified:

1. The first page of the insert stated that Vibramycin had several useful properties not observed with previously available tetracyclines.

2. The medical review had noted the importance of adhering to the recommended dosage because of greater absorption and longer persistence, yet the insert said that the drug had been given to volunteers for long periods at high doses without evidence of toxicity, a statement which deemphasized the importance of following the recommended dosage.

3. The insert claimed the drug was useful in acne, whereas the medical review had noted that the studies in acne included only a few cases and lacked objective criteria for evaluating improvement.

Dr. Ley, the then Director of the Bureau of Medicine, called the company, discussed these points, and told them the product would not be approved until these issues were resolved. At a meeting on Monday, July 31, Pfizer representatives continued to protest these changes, contending they had been made after the company had been given informal approval of the package insert. They confirmed their objections in writing. However, the matter was resolved by the company agreeing to make the necessary changes, and on August 10, 1967, the certification monograph was published.

Mr. GORDON. Doctor, may I interrupt at this point?

Dr. MINCHEW. Yes.

Mr. GORDON. The application for Vibramycin, I notice, was submitted on June 22, 1966. The certification monograph was published on August 10, 1967. Now, if the claims for the product had not been so broad, is it reasonable to assume that it could have been put on the market much earlier?

Dr. MINCHEW. I think that is a fair statement, Mr. Gordon. I would not be able to pinpoint exactly at what point the approvability would have been implemented, but I believe the testimony indicates that a significant part of this last few months was dealt in discussing and negotiating over labeling.

Mr. GORDON. It does take a long time to negotiate, is that correct? Could that be the answer to the problem that Senator Hatfield was discussing a short while ago, that the firms make claims which you

try to cut down; the firms then are reluctant to accept your views and all this takes a long time? Is that the way it works?

Dr. MINCHEW. Yes, sir.

Mr. GORDON. And is that the way it is working with the other tetracyclines also?

Dr. MINCHEW. That is the way it is working with the other tetracyclines in that part of the negotiations that I have been involved in.

Again, I would like to check with the operating division involved in terms of where they are at this point in time with it.

Mr. GORDON. I want to push this a little further. Now, if the company had accepted what you wanted it to accept with respect to Vibramycin, then there wouldn't have been any problem; is that correct?

Dr. MINCHEW. There certainly would not have been the delay of these last few months.

Mr. GORDON. Concerning the delay in relabeling the other tetracyclines, if the firms said "OK, we will accept for the other tetracyclines what you suggested for Vibramycin," but they didn't do that: is that right?

Dr. MINCHEW. To date, as far as I am aware, we have not gotten concurrence from the manufacturers of the varieties of tetracyclines. We have not gotten concurrence with all of the changes we believe are necessary. I would, however, have to confirm the latest negotiations between the Bureau and the companies because I was not personally involved.

Mr. GORDON. So it is really the companies who are not accepting the FDA's recommendations and that is causing delay. Is that a fair statement?

Dr. MINCHEW. That is part of the delay. We do have our own problems in terms of staffing and priorities, but that certainly is one of the causes of the delay; yes.

Senator NELSON. As to the question though, of animal thyroid effects that you have required Pfizer to include in its package labeling, there is no necessity for any negotiations with the rest of the companies on that point; is there? You have made the decision that Pfizer must do it. Then I assume it is automatic that the rest of them have to do it.

You don't need to waste any time negotiating. You have settled that issue; isn't that correct?

Mr. GOODRICH. If we took the regulatory step of taking all products off the market immediately.

Senator NELSON. I don't mean taking them off the market. All I am saying is as to this one, I understand there are apparently several points that are involved in revising the package labeling, but you have settled so far, I assume, as all tetracyclines are concerned, you have settled the question of requiring that some notation be made of the animal thyroid effects in Vibramycin. Therefore, you needn't waste any time negotiating with another dosage form of tetracycline, wasting time back and forth with companies as to whether they agree that that ought to go in, do you?

Mr. GOODRICH. But the point is that if you made them make that change, which is a relatively minor change compared with others that are under discussions with the companies, you would not have achieved the rewrite of the total tetracycline package labeling that is now under negotiation.

This drug is also under review by the National Academy of Sciences, National Research Council for effectiveness. This is another factor that enters into the ultimate development of a final package labeling form. These are the procedures that Senator Hatfield asked about.

We could, of course, withhold certification of all the tetracyclines until this labeling change was made. This is what was done, of course, in some other instances with antibiotics. This was not regarded as that type of a hazard that should be called immediately to the attention of the profession through that type of action.

Instead, we thought it justified discussions with the companies with a view of developing a uniform pattern of labeling to be fully informative, accurate, and would have the necessary warnings in it. Of course, all of us will agree it has taken too much time.

Senator NELSON. So if I understand correctly what you are saying, that the requirement in the labeling of Vibramycin, which at the time the issue was raised was a new dosage form——

Mr. GOODRICH. Right.

Senator NELSON. Coming on to the market.

Mr. GOODRICH. Right.

Senator NELSON. For the first time, you had the information then that there were some animal thyroid effects, and you were requiring that that be included in the labeling in the first instance in the marketing of this product, right?

Dr. MINCHEW. Correct.

Senator NELSON. And you are saying that there are a number of other revisions that are apparently going to be made in the package inserts. They are under review. And so you had the choice of requiring everybody to change his package insert as to this one item.

Mr. GOODRICH. Yes, sir.

Senator NELSON. Or waiting awhile until you could settle all the other issues involved?

Mr. GOODRICH. That is correct.

Senator NELSON. And you are saying that you didn't consider it important enough under the pending circumstances to require them to make this specific amendment as to the animal toxicity question, and then a few months later another amendment to the package labeling? Is that what your testimony is?

Mr. GOODRICH. That is correct, sir.

Dr. MINCHEW. However, similar problems developed with the promotion of the drug.

Senator NELSON. Please go ahead.

Dr. MINCHEW. The first promotional material submitted to us for the initial campaign for Vibramycin included a 22-page "visual aid" to be used by detail men in explaining the drug to physicians.

Such a "visual aid" is particularly important because, among other reasons, it sets a proper basis for oral presentation to physicians by the company's detail men.

In preparation for a meeting between Pfizer representatives and members of our Division of Anti-Infective Drugs on August 15, 1967, Pfizer brought in a draft copy of the "visual aid" on August 8. This draft was discussed in a preliminary manner with Pfizer representatives and it was apparent that there remained a number of differences between us as to how Vibramycin should be promoted. The Division of Anti-Infective Drugs indicated to Pfizer representatives that the

material would be reviewed in detail and agreed to meet with Pfizer when the review was completed.

During the August 15 meeting, a number of specific changes in the visual aid were discussed, but not all of the changes that we recommended were reflected in the next draft presented by Pfizer in type-written form on August 16, 1967, a copy of which I have submitted.¹ Oral tentative acceptance was given by the Division of Anti-Infective Drugs to the revised copy, but it was also pointed out that other FDA approvals would be required.

Senator NELSON. What do you mean by that?

Dr. MINCHEW. That the Division to which this material was submitted and the initial reviewers did not have final approval authority.

Senator NELSON. So the Division of Anti-Infective Drugs gave a tentative oral approval of the proposed promotional advertising with a caveat that the final approval would be required by what other department?

Dr. MINCHEW. If it's promotional labeling or promotional advertising or general advertising, it also is reviewed by the Division of Medical Advertising. Final approval for either a New Drug Application or a supplement to a New Drug Application has been vested in the Office of the Director of the Bureau.

Senator NELSON. Well, at this stage in history, had there been an approval of the NDA?

Dr. MINCHEW. Yes. The monograph had been approved on August 10 and the labeling in the package insert was disapproved. Once the monograph is published in the Federal Register, the company is then free to submit for certification batches of the antibiotic.

Senator NELSON. But we are talking about some promotional material.

Dr. MINCHEW. Right.

Senator NELSON. That has nothing to do—is that right?

Dr. MINCHEW. Yes.

Senator NELSON. So what is the practice? Once there is an approval of the NDA, and they are certified to go into the market, are they required then to submit to you, they are required to meet your standards for the package labeling, but you are talking about some other promotional material, aren't you?

Dr. MINCHEW. Correct.

Senator NELSON. Are they required to submit to you all other types of promotional material for approval?

Mr. GOODRICH. What we are talking about, Senator, as pointed out in the statement, is a visual aid used for detailing. This is a piece of material the company brought in just at the final stages to go over with us, to make sure that this visual aid would be all right.

Senator NELSON. This is after the NDA.

Mr. GOODRICH. That is right. This was after the NDA had been approved for this antibiotic and the visual aid was brought in to be reviewed. They are required under the recordkeeping and reporting provisions to submit to us on a regular basis all of the promotional material used.

¹ See information beginning at p. 3568, *infra*.

They are not required to submit duplicative pieces that are substantially the same as one that has been previously submitted and approved. But this was a new piece which was submitted. It was examined by the Division of Anti-Infective Drugs, examined later by the Division of Medical Advertising, as the statement shows, and examined by the Director of the Bureau.

Senator NELSON. The law requires that all of this type of promotional material be submitted prior to its use?

Mr. GOODRICH. The law requires that the company submit such records and reports as are required by regulations. Our regulations do require that the companies submit on a regular basis for certified antibiotic promotional materials that are being used and that they obtain approval.

Now after a piece has been approved, the companies are entitled to use substantially the same presentation without reclearance to keep us from getting smothered in a mass of promotional material, but if the marketing piece has any significant change in it, they are required to submit that for approval. These are in accordance with the record-keeping and reporting regulations.

Senator NELSON. So at this stage in the testimony, they have had oral approval; is that correct?

Mr. GOODRICH. No; the drug had been approved. We had gone over the package insert labeling with them carefully. The monograph had been published, I believe; had it not, Dr. Minchew?

Dr. MINCHEW. Correct.

Mr. GOODRICH. And the product was ready for marketing. The company was concerned in August with going over with us this visual aid that would be used to launch the drug with the medical profession. As it turned out, it was quite important that we did have an opportunity to go over this with them to make sure that the drug was promoted to the profession in the way that we had agreed upon with the company. As the testimony develops here, there were still, notwithstanding the points that we had had differences with the company during July, there were still some differences over this visual aid, which were worked out.

Senator NELSON. Please go ahead.

Dr. MINCHEW. The draft submitted by Pfizer on August 16 was further reviewed within the Bureau of Medicine, including the Division of Medical Advertising, and a number of additional changes were found to be necessary. A meeting was held at the Bureau of Medicine on September 5, 1967, to discuss this draft. At this meeting, Pfizer unexpectedly informed us that they had already printed this four-color visual aid in final form on the basis of the tentative acceptance by the Division of Anti-Infective Drugs. A copy of this was also submitted this morning.¹

Such action on the part of a company to final print material prior to actual approval of a draft creates a subtle type of pressure to approve it, or at least to hold the required changes to an absolute minimum.

Senator NELSON. What were these changes? I had thought that there was tentative acceptance given by the Division of Anti-Infective Drugs to the visual aid; is that correct?

¹ See information beginning at p. 3574, *infra*.

Dr. MINCHEW. Yes; I will go into the types of changes. On the documents that I have submitted, you will notice the types of changes required as paste-ons.

Senator NELSON. These weren't proposed changes, then, that were called to the attention of the company by the Division of Anti-Infective Drugs?

Dr. MINCHEW. Not at that point; no, sir. The Division of Anti-Infective Drugs does not have the responsibility for the comment on the promotional material per se. It is only reviewed there because this is where the medical expertise reviewed the New Drug Application and the package insert. The promotional implications of the material itself, however, is the primary responsibility of the Division of Medical Advertising.

Senator NELSON. So at this stage the Division of Anti-Infective Drugs apparently discovered——

Dr. MINCHEW. They did not raise any——

Senator NELSON. Did not discover any claims—medical claims—over and beyond what they thought there ought to be? Is that assumption correct?

Dr. MINCHEW. I think the types of problems that we asked for correction will be seen better as we go on.

Senator NELSON. All right.

Dr. MINCHEW. We explained that the visual aid was not acceptable as submitted and that it would need revision. We pointed out that our comments regarding this promotional piece were parallel, and in principle similar, to those previously made by us to the firm in connection with Pfizer's advertising activities for a similar product, Randomycin. We proceeded to discuss with Pfizer representatives specific objections to the visual aid copy, page by page.

Among the important changes we requested were, that it be clearly specified that the once-a-day dosage was only a maintenance dose and that this dosage must be doubled in initiating therapy and for serious infections; that Vibramycin should be properly identified as another new member of the tetracycline family; that it be clearly stated that the antimicrobial spectrum of Vibramycin is comparable to other tetracyclines; that the need for culture and sensitivity of infecting organisms be pointed out; that use of data from clinical studies be limited to those cases in which sufficient cultures and sensitivity studies were carried out to demonstrate the effectiveness of the drug; and that a claim be dropped that suggested that less Vibramycin would be bound to bones or teeth than is the case with older tetracyclines since there was insufficient data to show this.

However, Pfizer informed us that they had already arranged for its detail men to gather for training sessions in preparation for the later marketing of the antibiotic. Many were en route to these sessions as we were meeting on September 5. They requested that they be permitted to use the uncorrected visual aid for these sessions. We agreed to this, provided Pfizer made clear to its staff the important revisions that were to be made before the aid could be used in detailing.

Mr. GORDON. Is there any evidence that Pfizer did actually make this clear to its staff?

Dr. McCLEERY. Dr. Minchew is reluctant to comment on this because I was involved directly in these negotiations, and as a general answer

to your question I would say yes. If you want to go into the details of why we think so, it will take some development, but I would say yes.

Mr. GORDON. There is evidence that they did make it clear to the detail men?

Dr. McCLEERY. There is indirect evidence that they did make it clear, yes.

Dr. MINCHEW. We were assured that this would be done. At the end of the meeting the senior Pfizer executive present, stated that in general the firm accepted FDA's proposals, and that the firm would prepare corrected copy for the visual aid and submit it to the Bureau of Medicine for approval as soon as possible.

Senator NELSON. This visual aid was to be used in detailing to physicians?

Dr. MINCHEW. Yes. Now, at this point in time the visual aid was going to be presented to the detail men themselves for instructional purposes for them, and then subsequently the visual aid would be used for the detail man's presentation to the physician.

Senator NELSON. All right.

Dr. MINCHEW. On September 11, 1967, Pfizer submitted a copy of the four-color printed visual aid with only some of the requested corrections pasted over the original copy. Several additional changes were considered necessary. Notable among these were: (1) The need to reduce from 754 to 454 the number of cases cited in a chart showing clinical success rate, since a number of the cases included by the company were not regarded as sufficiently documented; and, (2) The need to state clearly that claims for lower binding of calcium with Vibramycin were based only on in vitro studies.

These additional changes were discussed with Pfizer representatives, and they agreed to all of them. They were told that other promotional material, such as the file card, a booklet, and dosage calculator that Pfizer had presented, would have to be similarly revised before they were distributed.

In a letter dated September 14, 1967, Pfizer reflected its agreement with the changes we felt were necessary.

This submission is presented to you, and the paste over will show the necessary changes.¹

A revised, final printed copy of the visual aid was submitted on October 6, 1967, and a copy of this has been submitted.² It was reviewed and found to contain all changes requested in the prior negotiations.

Let me again note two of the major corrections Pfizer was required to make in the Vibramycin visual aid: First, the company was required to indicate that the antibacterial spectrum of Vibramycin was not significantly different from other tetracyclines; second, the company was required to omit, because of a lack of supporting clinical evidence, any inference that the depicted in vitro test indicated there was less chance that Vibramycin will be deposited in the teeth and bones of children.

Very soon after the introduction of the new antibiotic, a pediatrician reported to the FDA by letter that at the American Academy of Pediatrics annual meeting at the Washington Hilton Hotel, on October 25, 1967, a Pfizer representative had stated that Vibramycin in vitro had the least calcium binding capacity, and that, based on this

¹ See information beginning at p. 3596, *infra*.

² See information beginning at p. 3619, *infra*.

test, there was predictably less chance of human tooth staining with Vibramycin than with any of the other tetracyclines. This episode was followed up by the FDA and on December 8, 1967, an affidavit was obtained in which the physician stated, in addition to the above, that the detail man also stated that Vibramycin was more effective over a larger spectrum of bacteria, including certain staphylococcal and pseudomonal species, than were other tetracyclines.

A Bureau of Medicine physician, who is also a pediatrician, was in attendance at the American Academy of Pediatrics (AAP) meeting on October 25, 1967. He, too, was told by Pfizer representatives that there was predictably less chance of tooth staining with the Vibramycin and that Vibramycin was effective against certain organisms which were not susceptible to other tetracyclines. Staphylococcus and pseudomonas were specifically mentioned.

In addition, a letter was sent to the FDA from an assistant professor of pediatrics of a university medical school. He stated that at the American Academy of Pediatrics meeting in October it had been suggested to him by a Pfizer representative that Vibramycin would not cause tooth staining in children.

On December 22, 1967, the then Commissioner, James L. Goddard, called the president of Chas. Pfizer & Co., Inc., and informed him of these reports. This was followed by a letter from Dr. Goddard explaining FDA's objections in detail.

On December 22, 1967, a telegram was sent by the general manager of Pfizer Laboratories Division to all district managers, regional managers, and regional operations managers. The telegram, which was to be read to the company's field force, stated in part that:

1. "There is no evidence that Vibramycin does not cause tooth staining. To the contrary, as a tetracycline it must be assumed it does though no cases have been reported to date."

Senator NELSON. No cases of discoloration from Vibramycin?

Dr. MINCHEW. From Vibramycin.

2. "As a tetracycline, Vibramycin has essentially the same spectrum of antimicrobial activity as other tetracyclines. Claims of broader spectrum are not in accord with the evidence known to us at this time."

Vibramycin illustrates three problems which confront the FDA in approving a new drug for marketing. They are: first, the necessity for a most careful and critical evaluation of the data offered to establish the parameters of safe and effective use; second, the proper translation of the scientific data into labeling claims and warnings that will provide adequate prescribing information; and, third, the problem of improper promotion through oral detailing, despite extensive efforts in arriving at a complete understanding between FDA and the company as to the proper scope of the basic printed detailing piece.

Thank you for your attention. My associates and I will gladly attempt to answer any questions you may have.

Senator NELSON. We have had over the past year and a half at various times testimony about claims made by detail men that go beyond the approved claims authorized by the FDA in its package inserts and so forth. There have been studies that indicate that the detail man is a very influential force on the prescribing practices of the physician. This recognizes that some physicians don't have anything to do with detail men. I know some. It also recognizes that many

physicians rely very heavily upon the information given to them by detail men. We have had some dramatic cases including testimony here by a doctor who was told by a detail man that chloramphenicol did not have any serious side effects, when the same detail man had given notice to the community pharmacist that there had been something.

I think it presents a very serious problem. If the detail man is as influential on the prescribing practices of a large number of physicians as it appears he is, what method of control over what he presents to the physician can the FDA have, or what method should they have, or what should we do about it?

Referring once again to chloramphenicol, here is a most dramatic case of overpromotion through advertising and through the detail man had been called to my attention, achieving a situation in which distinguished experts testified that 90 percent and as high by one witness, as high as 99 percent of the people receiving chloramphenicol are receiving it for nonindicated cases, acne, infected gums, infected toenails, upper respiratory diseases, sore throats, headaches, all of them nonindicated, all of these cases exposing the patient to aplastic anemia, and a number died who received it for insignificant minor infections.

Yet the company was able to move into the marketplace through promotional advertising, through claims of the detail man, and sell at least 90 percent at the smallest estimate of its drugs for nonindicated cases. There were lawsuits with big claims, big judgments for misprescribing.

Dr. Goddard testified that he was at wit's end, to use his phrase, as to how to persuade the doctors to stop misprescribing this drug. The American Medical Association apparently was absolutely ineffective if it had any interest in trying to dissuade the doctors at all. It has been a great tragedy. Nobody knows how many thousands of people died from aplastic anemia that were not reported, because in those cases where chloramphenicol was prescribed for a minor infection, and the patient got aplastic anemia and died, they aren't reported. There is a good reason for not reporting them. There is no record-keeping. There is no central reporting. The physician who did it and discovered he had made a mistake is not going to report it. So we don't know how many thousands and thousands of people died from it that were unreported, and how many more thousands ended up with a suppression of the capacity for producing blood cells, and remain ill the rest of their lives.

This can happen with the next drug and the next drug and the next drug. In this case the medical profession, the American Medical Association in particular, should have been screaming at the top of its voice. Nothing was done; nothing effective, anyway. Nothing effective happened until we had extensive hearings on it and until there was widespread publicity.

The FDA sent out 200,000 letters, and stories were appearing all over the country, and then from that the batch certification dropped, January 30 through June 1967 it was 20 million grams, and January through June of this year 4 million grams. It is just an incredible story to me. It took a congressional hearing to dramatize the case, and if there hadn't been a congressional hearing on this thing, there would be 4 million people a year getting chloramphenicol, 90 percent at least, according to Dr. Dameshek and as high as 99 percent, according

to others, getting this very potent, dangerous drug. It wouldn't have been stopped by FDA; it wouldn't have been stopped by the AMA, which would continue to take ads for chloramphenicol saying, "When it counts, use chloramphenicol."

I think the whole business is a disgrace and a real shocker that ought to scare every person in the United States.

Now, what has the FDA got in mind about suggesting what we do about controlling the advertising so it does not overpromote and controlling what the detail man says to the physician? On that aspect of it, at least, we ought to get some recommendations from FDA.

Now, the continuing education of the doctor, that is something that I don't expect is your business. That tremendous failure is the fault of the medical profession, and it is a terrible indictment in my judgment. But I would like to know what we are going to do to keep another chloramphenicol case from occurring in this country, and with the present company saying, "Well, the usage of the drug dropped off because of the hearings but it will come back again." What he means to say is, "We will promote it again, and we will have people dying from aplastic anemia for a prescription of chloramphenicol for an infected tooth or acne or hangnail." That is what was happening, and the company is willing to do it again. I don't know what kind of standard of ethics is followed by this company, by business people, but it seems to me the FDA has got some positive responsibility to take this fight head on, if you are going to protect the public interest. I don't know who else is going to do it.

The Congress isn't qualified to do it. It is just by accident that this chloramphenicol case came up at these hearings, but it takes the expertise of the people in the field to do this, and I don't know how it is going to be done. It seems to me the FDA ought to do something about it. You have the expertise. I would like to know what you think ought to be done about it. The advertising of this drug is ridiculous. The FDA knows about the testimony before this subcommittee by Parke, Davis that: "We don't list any side effects at all of Chloromycetin in England because the law doesn't require it. We don't list any other country because the law doesn't require it."

When we asked "Why not," the company's representative said, "We comply with the law of the country in which we sell," all of which means, "We can promote it over there and make a profit on the deaths of other people."

I think something has got to be done about this business, and I would like to know if FDA has some ideas about controlling the promotion of these drugs so the doctor isn't misled, because the fact is, the hard, cold, sad fact is, that the great, distinguished American medical profession in substantial numbers is being misled by promotional advertising and detail men, and the proof is in the record abundantly. This is a grave reflection on the American medical profession, not all of them of course, but it is a reflection on the medical profession just in the chloramphenicol case alone. How do we know that there isn't another case like this coming?

I would like to know what the FDA's ideas are for legislation or something, regulations to be proposed to the Congress. You have got the expertise. We don't.

Maybe that isn't your function. It may be an unfair question. I address it to the whole of FDA. I suppose it is Dr. Ley's responsi-

bility, but I don't think anybody who knows the facts, any American citizen, can help but be shocked and ashamed at what is going on in the promotion of drugs for purposes for which they should not be used, just for the purpose of making a profit. I think that is a terrible, terrible thing.

When I look at that stack of letters in my office from parents whose kids got chloramphenicol, 18-year-olds, infected tooth, hangnail, sore throat, my heavens, what are we coming to if that is what we will do to make a profit? And what is happening to regulations in this country, if the FDA with all of its physicians can't come up with some recommendations as to what we should do? Maybe we ought to get rid of all detail men. If that is the result, maybe we ought to stop it, just not have it. If this is the best we can do, we ought to stop them. Maybe you ought to stop this type of promotional advertising; make the physician go to a source to find out what that drug does; he should go to a reliable, unbiased source. Make them take some educational courses, continuing education of the physician. But I don't see out of the promotional practices—I see a negative in the detail man and the promotional advertising.

It shocks me, the stuff I have looked at, but I don't expect you to respond to that. That isn't what I called you up here for. But I expect to be calling upon the FDA for some ideas about this because I think it has got to be corrected.

MR. GOODRICH. May we respond just very briefly, Senator, to that. You know what our program was on Chloromycetin. We did send out the letters as you know, and we sent letters to the physicians and to the hospitals and others.

Senator NELSON. Are you talking about the Chloromycetin letters?

MR. GOODRICH. Yes, sir; after the hearings, and it did have an effect. This matter of oral detailing of Chloromycetin was reviewed by Senator Kefauver's committee back in 1961. At that time we did not have inspection authority over this kind of information. Nonetheless the Commissioner did take it up with Parke, Davis and within the limits of what he could do with voluntary compliance efforts were made to stop this. This is not to say that oral detailing isn't a problem.

You asked what has Food and Drug Administration done and implied that the total picture or presentation of information to the physicians is totally bad. With that of course we must disagree.

Senator NELSON. I didn't say it was totally bad, but all I am saying, if I may interrupt, Mr. Goodrich, is that in the promotion of chloramphenicol, through advertising and detail men, 4 million people a year were being prescribed that drug when it shouldn't have been—well, the highest figure by Dr. Damashek was 100,000, maybe, and that was the effect of the promotion and advertising.

If you will look at the sales record over the years, after the Kefauver hearings and at various times, it fluctuated up and down a bit, but the first time it dramatically dropped was after our subcommittee's hearings, and in comparing the first 6 months of last year versus the first 6 months of this year. What are you going to do if it gets back up to 40 million grams a year again?

MR. GOODRICH. What the Commissioner committed himself to do, and I am certain that it will be done, is to follow the production and certification of that drug in a regular way, on a regular basis, so that if its certification and sales do grow again, then the message must be put out

again, or we will have to reconsider whether or not the product should remain on the market. But the agency is alert to Chloromycetin, and has exercised efforts over the years to hold its prescribing within bounds. There is no question that it did get out of bounds.

I was trying to address myself to the broader question of what have we done on the overall issue of promotion. In 1961, we put out requirements for full, complete disclosure to physicians on all promotional pieces. This made a drastic change in the information that went to the prescriber.

In 1962, Congress gave us authority over effectiveness claims, that was a program to review all the claims that had been approved over the years. The program of reviewing the claims is underway. Soon after the enactment of the 1962 amendments, we required drastic changes in the advertising. That is still a matter of controversy with us, but some steps have been taken to improve this, not enough, of course.

Senator NELSON. All I am saying, however, is the great and dramatic failure was chloramphenicol, because it continued to be prescribed indiscriminately. Nine out of 10 people for whom it was prescribed shouldn't have gotten it.

Mr. GOODRICH. Dr. Goddard could see to that when it came up.

Senator NELSON. What I am concerned about now is by what mechanics do we prevent it from happening again. The FDA, maybe through no fault of its own—whatever it required on the package labeling—was not effective. It didn't work. And I would have thought, knowing what the FDA did know, that your "Dear Doctor" letter should have gone out saying that nine out of 10 of you fellows prescribing this drug are prescribing it for nonindicated cases, and you had better stop. That is what I think should have been done. I assume that the FDA knew that people were dying from a drug that they shouldn't have received in the first place, and this went on for years and years and years. Just think of the tragedies. But FDA did nothing effective about it.

Yesterday we had Indocin, and the usage is contraindicated in children on the label clearly as can be. Yet 10 percent of pediatricians in a poll said they used it in children. They are misprescribing that drug. There is something wrong here, tragically wrong.

Senator HATFIELD. I have a couple of questions on the matter of restricting these drugs once they have been determined by your agency that they do not represent the truth, or to provide all the therapeutic value they claim. Take chloramphenicol.

Let's say that they decided to promote this drug again, and on the second go around you determine that it still lacks safeguards that you had prescribed or that you wanted placed on them. What would FDA do, negotiate, or what kind of action would FDA take against an industry or against a pharmaceutical house that violated what you considered to be appropriate safeguard requirements?

Dr. MINCHEW. Does your question pertain to total promotion or medical journal advertising or oral detailing?

Senator HATFIELD. Anything, any part of the promotional field which would tend to cause people to expect more and to submit themselves thereby to certain dangers than that which really exists?

Mr. GOODRICH. We have a variety of sanctions to deal with that, Senator. If the company made representations contrary to what had

been approved in advertising or promotion, it would be a criminal offense. We also have an administrative mechanism for discontinuing the certification of an antibiotic, where it is being promoted for conditions contrary to what has been agreed upon between us and the company in certifying the lot. Chloramphenicol is an antibiotic, so there are rapid mechanisms for dealing with such a problem.

Senator HATFIELD. Have you used that power that you have?

Mr. GOODRICH. Yes; we have.

Senator HATFIELD. Frequently?

Mr. GOODRICH. Not frequently, but it has been used decisively in a number of instances.

Senator HATFIELD. Have you used it more or less than opportunities provide? In other words, have you been conservative in the exercise of this authority, or have you been liberal?

Mr. GOODRICH. Quite conservative.

Senator HATFIELD. Do you feel that perhaps if you were a bit more aggressive or less conservative in your application of this power, it might be helpful in policing the industry that you are required to police?

Mr. GOODRICH. I expect the drug industry would say that we have been quite liberal in the exercise of the authority, but I think that, we hope that, we have struck the proper level of enforcement, but maybe we haven't been strong enough at some and perhaps too strong at other times. But there are mechanisms for dealing with the problem.

Senator HATFIELD. You feel you have adequate authority?

Mr. GOODRICH. Yes.

Senator HATFIELD. At this time, to deal with any situation that might arise in which you are called upon to protect the public?

Mr. GOODRICH. We think so. We examined our authority in great detail, when the Kefauver investigation was on, and made our recommendations. Now, since then, as you know, the President has recommended the enactment of legislation to provide for the issuance of a compendium which will provide one of the points Senator Nelson was talking about, that is, an on-the-desk, authoritative unbiased viewpoint of drug prescribing information.

Congress hasn't acted on that yet. But we are hopeful that something can be done.

Senator HATFIELD. On the matter of keeping control over the promotional program of these pharmaceutical houses, what is and what is not included in your review as far as promotion materials are concerned?

Mr. GOODRICH. Both the package material, all direct mailing, catalogs, movies, tape recordings.

Senator HATFIELD. Charts?

Mr. GOODRICH. All that, charts, visual aids, all that material which has been classified, as we were authorized to classify it by the Kefauver-Harris amendments, as labeling requiring full disclosure.

We also have authority to regulate the advertising of prescription drugs, but not the advertising of over-the-counter preparations. We initiated our prescription drug advertising program early in October of 1963, soon after the Kefauver-Harris amendments were passed. The regulations were placed into effect, I believe, in January of 1964. They have been successful in bringing about significant changes in

general advertising for prescription drugs, but they still pose some problems.

Last year we took the initial steps to improve the quality of advertising messages. We received objections from pharmaceutical manufacturers and the advertisers and a lot of other people.

Senator HATFIELD. This was on a continuing basis?

Mr. GOODRICH. Right.

Senator HATFIELD. As well as on——

Mr. GOODRICH. To bring these regulations up-to-date to deal with the problems that had emerged under our experiences with the regulations placed in effect in 1964.

We highlighted in the revised regulations those points of most concern and the points of failure that we had seen in actual practice.

Now PMA opposed that, and notwithstanding, we have taken efforts to resolve our difficulties. The matter now stands that they have objections in and it will have to go to a public hearing.

Senator HATFIELD. So that you have both the initial authority to deal with their advertising and promotional material as they introduce a drug, and then the continuing responsibility.

Mr. GOODRICH. Yes.

Senator HATFIELD. To review any additional or modified or changed——

Mr. GOODRICH. Yes.

Senator HATFIELD (continuing). Modifications or changes in their advertising and promotional materials.

Mr. GOODRICH. Yes.

Senator HATFIELD. Then as I understand it, you have control over everything except what may be stated orally by the detail men?

Mr. GOODRICH. Well, the opinion that Senator Nelson put into the record yesterday from the Library of Congress indicates some doubt about our authority to deal with oral detailing of this kind. I have no such doubts.

As Senator Nelson's opening statement said, in 1961 when we promulgated the full disclosure regulations, we provided that a drug, a prescription drug would be regarded as misbranded unless its labeling contained adequate directions for professional use for all the conditions for which it was advertised or represented. Now, that included oral detailing. That regulation has been in effect since 1961, was specifically called to the attention of the Congress in 1962, and was recently sustained in a criminal case in Chicago on whether we had the authority to promulgate such a regulation. So I don't have the doubts and fears that the Library of Congress opinion does. I will be glad to supply the committee with our views, if you would like to have them in detail.

Senator HATFIELD. But the point I am trying to get at is, that actually unless there is evidence shown from the oral presentation by say, a detail man that he has misrepresented the drug to the doctor, it is difficult then to enforce or police other than that which you have as now the existing authority on the printed and visual and all the other kinds of——

Mr. GOODRICH. Sure it is difficult. There is no question at all about that.

Senator HATFIELD. Yes.

Mr. GOODRICH. And this is why we have put our priorities first on making all the public promotion that goes in such great volume, both

believable and informative. This was our advertising and full disclosure regulations.

Now, as we move into problems of detailing, no detail men sent us any bulletins. Senator Nelson sent us the bulletins. If some detail men would be good enough to send us the bulletins, we would know how to react to them.

Senator HATFIELD. Do you feel you have enough authority then in the area of—

Mr. GOODRICH. Of inspection.

Senator HATFIELD. Of inspection and review of promotional and advertising materials.

Mr. GOODRICH. I think we do, but of course there are going to be controversies over this.

Senator HATFIELD. Yes.

Mr. GOODRICH. We have taken some steps to learn more about detailing. The companies, some of them, take the view that this is a private matter that is none of our business. We, of course, couldn't agree with that. We think it is public business.

Senator HATFIELD. The law doesn't agree either with that viewpoint.

Mr. GOODRICH. Yes.

Senator HATFIELD. Now, in the case of chloramphenicol, did you approve this drug in its original presentation to the market?

Mr. GOODRICH. Yes, Senator.

Senator HATFIELD. Its introduction?

Mr. GOODRICH. That product was approved. We made a full statement on this before the committee.

Senator HATFIELD. Yes.

Mr. GOODRICH. It was approved, I believe, in 1949. By 1952, the first alarm had been sounded about aplastic anemia. We did have a review by the National Academy of Sciences and modified the labeling. That was reviewed again in 1961 at the time of the Kefauver hearings, and a further tightening up of the labeling was considered.

Senator Nelson was good enough to bring out that there were now available incidence figures of aplastic anemia to give us a measure of how often the aplastic anemia side effect occurred. This new information was incorporated into a much stronger warning to the profession, which went out, I believe, last spring.

Senator HATFIELD. So the original introduction of the drug was then under the approval of the FDA?

Mr. GOODRICH. Yes.

Senator HATFIELD. And that included the packaging instructions and claims?

Mr. GOODRICH. Yes, sir.

Senator HATFIELD. Made by the pharmaceutical house, and then you had also review of their promotional and advertising material as it related to this particular drug?

Mr. GOODRICH. Yes.

Senator HATFIELD. There were none of these things along the way then that would indicate to you that there had been misrepresentation?

Mr. GOODRICH. We knew from the oral detailing to one of our own physicians, I mean the issue of oral detailing was divulged by our own experience. One of our physicians on the west coast was detailed for chloramphenicol by one of Parke, Davis' people, and he was told

that notwithstanding what was in the labeling, chloramphenicol was no more dangerous than some other competing product.

The physician reported that back in here, and the Commissioner took it up with Mr. Loynd, the president of Parke, Davis. That exchange is in the hearings on the Kefauver investigation.

Senator HATFIELD. So it was in the oral detailing that the misuse or improper use of this drug was experienced that created some of these ill effects?

Mr. GOODRICH. At least in part, yes.

Senator HATFIELD. What I am trying to get at is, is there a lack of authority or breakdown in the relationship between the industry and the FDA and the doctors and what have you that could be precluded from arising again or finding another similar experience? Do you feel that the pharmaceutical house or the houses chose to promote this drug in an improper way or make this decision on the basis of economics rather than therapeutic value?

Mr. GOODRICH. I wouldn't like to judge their motives. I only know that from what we have seen, this drug, chloramphenicol, was grossly misprescribed. Nonetheless on the broader issue of detailing, we had no authority whatever to get into this in an inspection way prior to 1962. Now we have a lot to learn about detailing. As I said a moment ago, detail men have not favored us with these inside communications. We found, after we saw the material Senator Nelson submitted to us, a need to make some further inquiry into what was going on in the detailing. That project is underway, but is still in the preliminary stages, and we are not prepared yet to discuss it in any final way.

Senator HATFIELD. Could you enjoin an industry or a drug house, say, to stop immediately?

Mr. GOODRICH. Yes.

Senator HATFIELD. Do you have that power?

Mr. GOODRICH. Yes, we have that authority. We don't have the authority to enjoin them. We would have to of course seek——

Senator HATFIELD. Through the court?

Mr. GOODRICH. Court, yes.

Senator HATFIELD. But you have the authority?

Mr. GOODRICH. We do have the authority to seek a statutory injunction.

Senator HATFIELD. It seems like we have two very important problems here to resolve at least in my clear understanding that perhaps would be helpful for the record. We have two specific problems. One is the relationship of FDA to the industry, to the practice of medicine as it relates to the matter of protecting the public against drugs that would be harmful. As I understand it, you feel you have existing authority sufficient to deal with this.

Mr. GOODRICH. We think so.

Senator HATFIELD. So when something like this arises, then as far as that part of the problem is concerned, you feel you could act upon it adequately and quickly enough to protect the public, such as the chloramphenicol situation?

Mr. GOODRICH. We think we have the authority. Now whether we are alert enough, whether we exercise our authority quickly enough, or whether we are diligent enough in our investigation, are human issues, but the law is there.

Senator HATFIELD. The second point it seems to me then that needs to be clarified is how then do we deal with the problem of oral detailing? Do we do this with new alternatives to oral detailing? Is there some other approach here or some other technique that can be used in order to bring about a tightening up or a greater control, because as I understand it in the chloramphenicol case, you described the oral detailing as one of the bases of this great disaster. How do we correct that or how do we find an alternative to that problem?

Mr. GOODRICH. We are attempting to correct it first by insisting that all of the written, printed, and graphic matter, both the direct mailing, the tapes, and the motion pictures and all the other promotion, give the physician a full disclosure of the good and the bad that can be expected from the drug.

We are proposing to correct it by being sure that the advertising copy, which runs in great volume, tells the physician accurately and adequately what the hazards and the benefits of the drug can be.

We are trying to improve the advertising regulations.

Now, when we get down to the issue of oral detailing, our first program is to learn more about detailing. We have that project underway. If we find bulletins of the sort that were introduced yesterday and found that they were authorized by the company, we would have authority to take immediate action on that.

Senator HATFIELD. In this situation that you bring up, what do you feel about this increasing or at least it appears to me to be an increasing activity on the part of the industry to advertise directly to the public? And it is not perhaps carried in trade journals and other medical publications.

Mr. GOODRICH. Our view, Senator, has been that in general, prescription drugs ought to be advertised to the profession. The oral contraceptives, however, have introduced something new here, in which the companies have an inclination or desire to advertise the products directly to the public.

We issued a statement of policy on this, saying that where a company decided to advertise a prescription drug directly to the public, it would nonetheless have to have a proper disclosure of adverse reactions as well as indications in terms that were understandable to the nonprofessional audience.

We haven't seen a great deal of direct advertising of prescription drugs to the patient, but the oral contraceptives have introduced that problem, and we have a statement of policy on it.

Senator HATFIELD. How long does it take on the average for your agency to stop a certain advertising practice?

Mr. GOODRICH. Not very long. During the last 2 years we have met with companies on, I believe, 26 or 27 occasions to discuss with them advertising failures. Each one of these were episodes involving a Journal ad or, in two or three instances, labeling in the Physicians' Desk Reference, which we regarded as misleading and requiring immediate change.

I believe without any exception at all, the companies were willing to discontinue the advertising at once. We insisted on a mailing to the profession in general to bring about a correction, and in two instances we have called for the production of corrective advertising.

Senator HATFIELD. Do you consider then this case to be an exception,

the case we have had under consideration today, the length of time involved here? Is this exceptional?

Mr. GOODRICH. We were requested to present this case to give the committee something of the feel of what goes on between the agency and the sponsor in first assaying the clinical data to decide how good the clinical drug is and what can be expected of it, and what goes on between us in terms of developing a proper promotion. In this instance, there were two public-spirited physicians who called our attention to detailing that was beyond the approved labeling. This is not the usual experience for us, but this case was chosen by the committee staff to give some idea of how we were doing our job and what sort of pressures back and forth were involved.

Senator HATFIELD. By this committee staff?

Mr. GOODRICH. Yes.

Senator HATFIELD. But this would not be what you would call a typical case. If I understand you correctly from what you said, if you have a case in which you are concerned about the advertising practice, you could stop it just in the matter of days.

Mr. GOODRICH. This case, Senator, involved a drug about to be introduced into the marketplace. Where we have a drug that has been approved, the regulations on advertising say that you can only advertise an approved drug for the conditions that have been approved.

If we find in our surveillance of the advertising copy, such as we see in journals like the Medical World News or the Journal of the American Medical Association, our technique is to work up in a scientific way what we regard as the defects in it, to communicate with the company and go over with them the failures in that message, and to discuss at that time an appropriate corrective action.

Senator HATFIELD. What length of time does that normally take?

Mr. GOODRICH. That normally takes a very short time, the matter of a few days to a few weeks.

Senator HATFIELD. What I would like to make certain that I understand correctly, and if I do then I want to make certain that it is in the record as such, that this case as it has been presented to me impresses me as one in which the procedures are very clumsy, that it appears to me that there are a lot of examples in here of poor administrative practices. Let me just point out one or two.

When you had something very definitely questionable in your mind about the visual aid, you said to this industry, "Go ahead and present it to your detail men, but warn them." I mean it is like in a court when a witness has said something in front of a jury and the judge says "strike that." Well, it has already heard this. I think this is analogous.

Mr. GOODRICH. Let me just react to that in the real world. We were sitting down with Pfizer to go over this visual aid, and they suddenly present us with a final printed copy. We thought it was still in development. We said to them, "this visual aid is no good. It can't be used."

They say to us, "but we have all of our detail men coming to a meeting. Many of them are en route. Can't we use this as a piece and then explain that changes will be made?"

Whether for good or bad that was the human part of the decision.

Senator HATFIELD. I just couldn't disagree with you more. I think you have not only the authority, you have the responsibility to tell them no. Maybe it is not more law. Maybe it is a little more aggressive attitude toward the law that you now have.

Mr. GOODRICH. Perhaps so.

Senator HATFIELD. I couldn't be less interested in their logistical problem, if this film were inaccurately portraying a drug that you said should not be portrayed that way. You had a responsibility to deny them the use of that film.

I think, too, on the top of page 5, "the final review developed the fact that we did not have a firm understanding with Pfizer." I mean to me this is filled with procedures or practices that showed either lack of a strong position posture in other activities that I hope is not typical of FDA, because frankly from the testimony in this case, and I don't know why the staff chose this one, because it didn't help their side of the case at all in my opinion, this was not a case that would be typical, I would hope would not be typical.

What I would like to see is the aggressive posture of FDA in handling any of this advertising and promotional material on which they have doubts. And then, also, on the basis of equity as it relates to other companies, other competing pharmaceutical houses. But that is just a point of view that I have that I wanted to make sure that I understood and that I held on a certain basis of fact and that it is not an improper or not a factual understanding.

I would like to suggest, too, that on this whole matter, where we do have staff inadequacies, as indicated awhile ago, legal inadequacies or other such, I know that Senator Nelson is keenly interested in this matter. I, too, share his interest. There are many other Senators on the Appropriations Committee, and others, who would share the interests that we have.

We certainly would feel very pleased if you would indicate to us that we could become an ally to you in behalf of your financial needs before the Appropriations Committee, because we are interested in a policy and in the policing and the other activities of this agency. If you are inadequately staffed, you can't come before us and fulfill your responsibilities here. We have no reason to demand anything more than you are capable of performing.

But if you do have the law, and as you indicate to me, you have the adequacy of law to enforce, to administer, to police, then it seems to me there might be a review as to the philosophy of your agency's attitude toward these laws, philosophy and attitude toward these laws and administrative responsibilities, because I do feel that we should be most aggressive in this field, most aggressive.

Mr. GOODRICH. I would agree with you. Vibramycin, the big, the salient point that comes through, however, is that here is a drug which was introduced on the proper basis, once all these negotiations went through. Perhaps there was some laxity or unsatisfactory procedures as you see it, where we did not have a firm understanding. But the critical fact is that before this drug was launched to the medical profession, an accurate, informative, reliable statement of its place and its hazards was presented both in the labeling and in the promotional material.

Dr. MINCHEW. I would like to make one comment in regards to the first paragraph on page 5. The impact of this statement was not that it just all of a sudden dawned on us that we didn't have a final understanding. It was when this visual aid material was presented that the promotional thrust of the material did not reflect that we had reached this understanding in the negotiation of the package insert.

Senator HATFIELD. As I say, the implications may be in error, but it does seem to me that we have here an awful lot of negotiations, discussions, and involvement that I am sure are very technical and very difficult to handle, but I do think that the agency was in error in permitting the films shown, the visual aids shown, when it had to be predicated on a modification, oral modification by those who were showing it. It is just one of the, I think, sloppy procedures.

Dr. McCLEERY. It may well be true, Senator, but I think you might for your own sake, in talking in terms of reality, want to be aware of what it is we are talking about. I don't think you have seen and, therefore, couldn't understand what it is we are talking about. We are not talking about a film at all.

We have submitted the visual aid for the record, which I am afraid you haven't had the opportunity to see. The agreement to which you are taking some exception, is the agreement by the agency to allow the company to use it in the training session of their detail men. It was not an approval to use the visual aid when the product was on the market to be detailed to physicians.

What they were requesting was that since they had their detail men en route to a series of company meetings across the country, that, rather than to take some typewritten copy, they be permitted to use the printed visual aid. The men would later get corrected copies before they went out to detail physicians. This is the nature of what we are talking about.

Senator HATFIELD. You have not impressed me with your comment at all, because I think, and I stand corrected on whether it is a film or a visual aid, they should have received nothing, or they should have received something mimeographed. I mean a film certainly takes a lot longer to produce. If we are dealing now with just pieces of paper here, I mean that is all we are dealing with, it is attractively presented in color, and so forth.

But to let them go ahead and present this, I think, is even less excusable, less excusable when you found it objectionable. They should have either totally corrected it——

Dr. McCLEERY. They did.

Senator HATFIELD (continuing). Or eliminated it.

Dr. McCLEERY. They did totally correct it, Senator Hatfield. Let me just say that there is no film in this problem at all. There were very specific negotiations.

Senator HATFIELD. Well, we are in a judgment area rather than a factual area.

Dr. McCLEERY. If we are in a judgment area it would be nice to have the facts on which to base a judgment.

Senator HATFIELD. Yes; we have the facts here, and I think the judgment is still wrong on the part of the agency.

Dr. McCLEERY. You may be correct, but it might be helpful to get the facts before a judgment is made.

Senator HATFIELD. We have the facts here and the judgment has been made on the basis of facts, so the record will show that, too.

Any other comments or questions?

Dr. McCLEERY. Yes; I have a comment.

Senator HATFIELD. I think Mr. Gordon has some questions he would like to ask.

Mr. GORDON. In view of the care that the FDA exercised in regard to the detailing of misleading statements by Pfizer detail men, do you regard the matter as serious?

Dr. MINCHEW. The matter of the details over which we were discussing?

Mr. GORDON. Yes.

Dr. MINCHEW. Yes; I do. The difference of opinion that we had in regard to the antibacterial spectrum, I would consider serious. Any misinformation which the physician might have that this drug would be effective in treating staphylococcal infections which indicated resistance to other tetracyclines could be very serious.

I would also consider the tooth staining problem certainly serious. If the physician were misled into thinking that this were a tetracycline which did not stain teeth and he used it without this consideration, I think it would be a serious matter.

Mr. GORDON. If you believe this matter was serious why did you select the kind of regulatory action you took rather than some other forms of action?

Dr. MINCHEW. From the medical standpoint, the seriousness of this was such that we felt the most important corrective measure was to take steps to be certain that the physician did not get this misinformation, or it did not continue. It apparently had taken place at the American Academy of Pediatrics. This is why we took this step to most expeditiously determine as far as we could that the misinformation and oral detailing did not continue.

Now in terms of other legal steps that might have been available, I would like Mr. Goodrich to comment, if he cares to.

Mr. GOODRICH. The decision in this case was made by Dr. Goddard to call the president of Pfizer about the detailing. The Pfizer president immediately reacted to say that he would send a telegram the same day to all of this force to bring about correction.

That was done, and that was satisfactory to Dr. Goddard, who was responsible for the agency at that time. It was concurred in by me and by others.

Senator HATFIELD. Who made the decision to permit this visual aid material to be used?

Dr. MINCHEW. For the purpose of informing the detail men?

Senator HATFIELD. Yes.

Dr. MINCHEW. This was a decision made in the Bureau of Medicine.

Senator HATFIELD. By whom?

Dr. MINCHEW. Dr. Ley and me.

Dr. McCLEERY. Mr. Gordon, may I have the microphone again?

Senator HATFIELD. Just a minute. He had a series of questions. Just 1 second.

Dr. McCLEERY. Yes. I asked him if he would yield the microphone, Senator.

Senator HATFIELD. Well, I happen to be chairman.

Dr. McCLEERY. May I ask you?

Senator HATFIELD. Just a moment. Just as soon as Mr. Gordon completes. Will you finish your questions first and then we will be happy to.

Dr. McCLEERY. Thank you.

Mr. GORDON. What would be your attitude regarding new legislation that would make it a misdemeanor for any detail man or other representative of a firm to make a false or misleading oral statement about a drug?

Mr. GOODRICH. We wouldn't have any recommendation on legislation and couldn't until it went through the regular system, you know, through the agency, and so forth. But in terms have we considered that as a legislative need; we have not.

We have in regulations already the authority to classify a drug as misbranded if it is orally represented for a condition for which it is not labeled, and that would result in the product being misbranded and it would be a misdemeanor. So we would think that legislation you are talking about would not be necessary.

Mr. GORDON. You think it is covered now?

Mr. GOODRICH. I think so.

Mr. GORDON. How many legal actions has the FDA initiated in the last 5 years based on violations of section 502(f) (1) in advertising of prescription drugs?

Mr. GOODRICH. None, I believe.

Mr. GORDON. Can you tell us why?

Mr. GOODRICH. Because we have been concerning ourselves with the higher priority problems, one, with the full disclosure regulations, second with the advertising, third with review of effectiveness for all drugs approved between 1938 and 1962.

We have initiated an exploratory program into the field of detailing, and when those results are in, we will be ready to move into that area.

But we considered our first priority to deal with the adequacies and the truthfulness of the claims, and second, the kind of promotion that was going to the physician in great volume both in direct mailing and in advertising. That has occupied our attention in terms of priorities. We did learn about this oral detailing in the case of Vibramycin by a report from a physician, and the Commissioner took it up with the president of the firm.

Senator HATFIELD. Would you state your name, please?

Dr. McCLEERY. I am Dr. Robert S. McCleery. At the moment, I am Acting Deputy Director of the Bureau of Medicine, Senator Hatfield.

At the time of the events in question, I was in charge of the Division of Medical Advertising. I, too, am interested that the record be correct, and show the events and the nature of what it is we are discussing.

For the sake of the record, I think it should be pointed out in relation to your last statement, Senator Hatfield, that we this morning submitted a series of documents which I have reason to believe you have not had the opportunity to see.

The judgment that you reached as to the quality of the decision of the Bureau of Medicine in its agreement to allow Pfizer to use this in their training sessions I think could not be well informed until you had a chance to study the documents.

We feel that the record would show that the company made an agreement and that we have documentary evidence to show that we have reason to believe that the top management of the company kept its commitment to make sure that this improper detail piece was not used by their detail men.

Senator HATFIELD. Doctor, are these the documents you are referring to as it related to the involvement here as to whether there was judgment used in letting the company go ahead? Are these the documents you are referring to?

Dr. McCLEERY. Yes, but there are also some letters there which you have not had the opportunity to see, and I just wanted the record to show that I feel you have not had a chance to study the record.

Senator HATFIELD. These will be carefully studied.

Dr. McCLEERY. Thank you.

Senator HATFIELD. They have been studied enough to understand that they are visual aid materials that were not correct in their presentation, that is in their original presentation to you, and that you required certain changes to be made if they were to use them in their detail men's conference to introduce this drug.

Dr. McCLEERY. That is not correct, Senator, but go ahead.

Senator HATFIELD. And that they were to correct or make the corrections according to your requirements, according to Mr. Gordon, our man here, our counsel.

I am saying to you that based on the fact that these were materials which were presented even though they were in corrected form, as you have pasted little things in here, that I feel that there was a judgment, a poor judgment used in making these materials, using these materials that would not be a permanent part of the promotional program.

That is all I am saying, and I would hold the opinion that it was poor judgment by your agency or maybe by you personally, I don't know. But we are not dealing here with facts but a matter of judgment. I am just indicating to you in my judgment, you have obviously indicated to me what your judgment has been.

Dr. McCLEERY. Thank you.

Senator HATFIELD. Are there any other questions now or statements or comments?

Mr. Gordon, do you have anything else?

Mr. GORDON. No.

Senator HATFIELD. We will adjourn until tomorrow morning at 9:30 in the same room.

(The supplemental information submitted by Dr. Minchew follows:)

CHAS. PFIZER & Co., INC.,
New York, N.Y., August 16, 1967.

Re Vibramycin, § 148z.3 and § 148z.4.

ALAN E. SMITH, M.D.,

*Acting Deputy Director, Division of Anti-Infective Drugs, Office of New Drugs,
Bureau of Medicine, Food and Drug Administration, Washington, D.C.*

DEAR DR. SMITH: We are submitting for your review the proposed Vibramycin visual aid and the Vibramycin Dosage Calculator, which we intend to utilize in the promotion of Vibramycin.

Sincerely yours,

M. G. ADAIR,
FDA Liaison Department.

[Cover]

THE ABSORBING STORY OF VIBRAMYCIN^R DOXYCYCLINE

NEW FROM PFIZER RESEARCH

Vibramycin^R doxycycline once-a-day dosage.

Vibramycin is the newest advance in tetracycline research . . . a unique homolog of oxytetracycline and methacycline.

In dosage and absorption (caption for art) developed for efficiency.

Vibramycin^R (doxycycline)—an efficient oral broad-spectrum antibiotic in terms of . . .

Serum concentrations of Vibramycin peak at a rate which approaches that of a tetracycline I.M. injection indicating the great absorption from the G.I. tract.

Long half-life and slow urinary clearance of Vibramycin allow you to prescribe it on a one-dose-a-day basis after the first day.

The lowest daily dose of any oral tetracycline.

Minimal dose related G.I. side effects.

May be administered with meals or milk without loss of activity.

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include the following infections when caused by susceptible organisms.

The broad-spectrum range of Vibramycin^R (doxycycline) activity:

Site of infection	Indications	Pathogens (susceptible strains)
Ear, nose, and throat.....	Pharyngitis Tonsillitis Otitis Media Sinusitis	Pneumococcus Beta-hemolytic streptococcus Staphylococcus H. influenzae
Lower respiratory tract.....	Single-lobe pneumonia Multilobe pneumonia Bronchopneumonia Bronchitis	Pneumococcus Streptococcus H. influenzae Klebsiella pneumoniae
Soft tissue.....	Impetigo Furunculosis Cellulitis Abscess Infected wounds Paronychia	Staph. aureus Staph. albus Streptococcus E. coli Klebsiella-Aerobacter group
Genitourinary tract.....	Pyelonephritis Cystitis Urethritis	Klebsiella-Aerobacter group E. coli Enterococcus Staphylococcus Streptococcus Neisseria gonorrhoeae
Other areas:		
Ophthalmic infections.....	Gonococci Staphylococci H. influenzae	
Gastrointestinal infections.....	E. histolytica Shigella	Salmonella Pathogenic E. coli
Miscellaneous.....	Bacteroides Brucella Listeria Mycoplasma pneumoniae (Eatonagent, PLO) B. anthracis N. meningitidis Proteus	Donovania granulomatis Pasteurella Psittacosis Rickettsia H. pertussis C. welchii Treponema Pseudomonas

¹ In combination with streptomycin.

Note: Vibramycin (doxycycline) may be useful in the treatment of acne vulgaris and acne conglobata.

With Vibramycin^R (doxycycline) the lowest effective dose.

The Key: Efficient absorption . . . as reflected in high blood levels—even in the critical first hour.

After 45 minutes, Vibramycin blood levels are higher than those provided by I.M. injection of tetracycline¹ in 15 human subjects:

¹ During passage through the body a fraction of each antibiotic is metabolized thus lowering the amount of active antibiotic recoverable after an oral dose.

	Vibramycin 100 mg. (oral) mcg./ml.	Tetracycline 100 mg. (I.M.) mcg./ml.
After 30 minutes.....	0.727	1.111
After 45 minutes.....	1.013	.866
After 60 minutes.....	1.244	.751
After 75 minutes.....	1.405	.715
After 90 minutes.....	1.562	.702
After 105 minutes.....	1.494	.657
After 120 minutes.....	1.462	.842

As demonstrated by excretion studies in test animals urinary excretion study¹ indicates significantly greater G.I. absorption of Vibramycin—The percentage of the oral dose recovered in urine of mice relative to the amount recovered after an I.V. dose is 3.5—5 times greater than these other tetracyclines. Oral and I.V. doses were equivalent.

RELATIVE ABSORPTION VALUES

	Percent
Doxycycline	70
Methacycline	21
Demethylchlortetracycline	19
Tetracycline	13

With Vibramycin, antibacterial effect demonstrated in experimental animal studies—Survival Time Studies in mice reflect rapid therapeutic concentrations of Vibramycin^R (doxycycline) in the critical first hour of therapy.

THE TEST

1. Hundreds of mice were inoculated with an amount of bacteria that was known to be lethal without treatment (either, *Staph. aureus* or *Past. multocida*). The two groups were kept separate.

2. At one-half hour after the lethal inoculation, four groups of 10 mice each were taken from each group and an antibiotic was orally administered. The antibiotics given and the dosage administered are listed below.

3. The same procedure was followed at 1 hour after the lethal inoculation and at intervals as indicated on the charts.

4. After a waiting period of 4 days, the animals surviving in each group were noted.

5. From the percentage of animals surviving at the various time intervals between the inoculation of the lethal quantity of bacteria and the oral administration of each antibiotic, the Survival Time₅₀ was calculated. (Survival Time₅₀ is that time at which, with the dosage administered, 50 per cent of the animals would have survived.)

THE RESULTS

Pathogen : *Staph. aureus*.

Percent of animals surviving after 4 days.

	Oral Dose (mg./Kg.)
Time in hours from inoculation to administration of drug :	
<input type="checkbox"/> Vibramycin	6.25
<input type="checkbox"/> demethylchlortetracycline	12.5
<input type="checkbox"/> tetracycline	12.5

Note: Tetracycline was not administered at the one-half hour interval.

Pathogen : *Past. multocida*.

Percent of animals surviving.

	Oral Dose (mg./Kg.)
Time in hours from inoculation to administration of drug :	
<input type="checkbox"/> Vibramycin	12.5
<input type="checkbox"/> demethylchlortetracycline	50
<input type="checkbox"/> tetracycline	50

¹ During passage through the body a fraction of each antibiotic is metabolized thus lowering the amount of active antibiotic recoverable after an oral dose.

The Survival Time Studies, while involving a limited number of organisms, resemble the clinical situation in that the infection is well established before antibiotics are administered.

The conclusion:

1. An important factor in protecting test animals is the rapidly attained therapeutic concentrations of Vibramycin. (Mice infected with *Staph. aureus* are generally moribund about four hours after inoculation.)

2. Even at a fraction of the dosage of other tetracycline antibiotics tested, Vibramycin provided a greater and more persistent chemotherapeutic effect.

With Vibramycin^R (doxycycline)—Excellent therapeutic results in humans [over 90% clinical success rate]:

Diagnostic group	Clinical response			Percent success
	Favorable	Poor	Total	
Lower respiratory infections.....	172	11	183	94
Upper respiratory infections.....	143	11	154	93
Soft-tissue infections.....	133	8	141	94
Genitourinary infections.....	57	19	76	75
Venereal (gonococcal infections).....	175	14	189	93
Miscellaneous infections.....	31	3	34	91
Total.....	711	66	777	92

Note: For criteria used in evaluating results of therapy, see end of brochure.

Summary of side effects in patients treated with Vibramycin^R (doxycycline) not all of whom met the criteria established for efficacy:

Side Effect	Number of cases	Side Effect—Continued	Number of cases
Nausea	24	Flare-up of colitis.....	1
Vomiting	13	Glossitis	1
Diarrhea	8	Stomatitis	2
Photosensitivity	7	Nail discoloration.....	1
Dermatitis	4		

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

With Vibramycin^R—Minimal untoward reactions in the lower G.I. tract as confirmed by the occurrence of only 8 cases among the patients treated,

The Key: efficient absorption:

Since absorption of Vibramycin is high, a minimal quantity of antibiotic is left in the G.I. tract. This would suggest the possibility of a lesser likelihood of monilial or bacterial overgrowth.

Vibramycin:

With Vibramycin^R (doxycycline)—Lowe degree of binding with calcium than any other tetracycline analogue.

Per cent of binding with calcium¹ (Based on *in vitro* studies) with equal amounts of each antibiotic:

Vibramycin	19.0
Oxytetracycline	36.0
Methacycline	39.5
Tetracycline	39.5
Demethylchlor-tetracycline	74.5

This study would suggest that less Vibramycin is bound to bones or teeth.

With Vibramycin^R (doxycycline)—The lowest effective dose—once a day after the first day

The Key: Long half-life:

Half-life of Vibramycin is significantly longer than that of other agents—based on single dose studies:

Doxycycline 15.1¹ hours (4)

Demethylchlortetacycline, 12.7 hours (4)

Tetracycline, 8.2 hours (5)

¹ With multiple dosing, the cumulative half-life has been reported to be approximately 22 hours.

Vibramycin owes its long half-life to slow renal clearance— $\frac{1}{2}$ that of DMCT, $\frac{1}{5}$ that of tetracycline.

Average renal clearance (As a percent of creatinine clearance) :

Vibramycin, 12.0(4)

Demethylchlortetracycline, 26.8(4)

Tetracycline, 61.0(5)

With Vibramycin—Serum levels are therapeutic around the clock(1)

The Key : Efficient absorption and long half-life.

Average serum levels of Vibramycin in humans.

And Vibramycin levels usually persist 24–36 hours after cessation of therapy

With Vibramycin—absorption relatively unaffected in the presence of food or milk.

Plasma levels of doxycycline and DMCT after oral ingestion of the drugs, fasting, and with foods in human subjects.

(Adapted from Rosenblatt, J. E., Barrett, J. E., Brodie, J. L. and Kirby, W. M. M.(4)

After the first day of therapy . . . the only one-dose-a-day tetracycline in oral form.

Vibramycin^R doxycycline once-a-day dosage. In dosage and absorption . . . developed for efficiency.

VIBRAMYCIN^R HYCLATE CAPSULES DOXYCYCLINE HYCLATE

Day 1	Day 2	Day 3	Subsequent days
Usual adult dosage... 2 caps. b.i.d. (200 mg.). 2 caps/day (100 mg.)... 2 caps/day (100 mg.)... 2 caps/day (100 mg.)			

Note: Vibramycin^R Hyclate Capsules contain doxycycline hyclate equivalent to 50 mg. doxycycline. Available in bottles of 50.

Vibramycin^R Monohydrate for Oral Suspension doxycycline monohydrate.

Recommended dosage for children:

First day of treatment—2 mg./lb. of body weight divided into two doses.

Subsequent days—1 mg./lb. of body weight given as single daily dose or divided into two doses.

For more severe infections—up to 2 mg./lb. of body weight.

Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry power for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. (each teaspoonful), with a pleasant tasting, raspberry flavor : 2 oz. bottles.

Vibramycin^R (doxycycline)—an efficient oral broad-spectrum antibiotic in terms of . . .

Serum concentrations of Vibramycin peak at a rate which approaches that of a tetracycline I.M. injection indicating the great absorption from the G.I. tract.

Long half-life and slow urinary clearance of Vibramycin allow you to prescribe it on a one-dose-a-day basis after the first day.

The lowest daily dose of any oral tetracycline.

Minimal dose related G.I. side effects.

May be administered with meals or milk without loss of activity.

In dosage and absorption . . .
Developed for Efficiency

REFERENCES

1. Research data on file, Pfizer Medical Department, Pfizer Laboratories.
2. English, A.R. and Lynch, J.E. : Proc. Soc. Exp. Biol. Med. : to be published.
3. Clinical data submitted to F.D.A. Available to physicians on request, Medical Department, Pfizer Laboratories.
4. Rosenblatt, J. E., Barrett, J. E., Brodie, J. L. and Kirby, W. M. M. : Anti-microbial Agents and Chemotherapy—1966, pp. 134–141.
5. Kunin, C. M., Dornbush, A. C. and Finland, M. : J. Clin. Invest. 38:1950, Nov., 1959.

CRITERIA FOR EVALUATING CLINICAL RESULTS

UPPER AND LOWER RESPIRATORY INFECTIONS

*Soft-tissue Infections**Miscellaneous infections*

Favorable responses: Includes those designated as "good" or "satisfactory."

Good—patient showed definite favorable response to doxycycline therapy with prompt alleviation of symptoms.

Satisfactory—patient showed beneficial response, but the duration of symptoms was longer than might have been expected with a good response.

Poor responses: Cases in which it was felt there was no response, or a worsening of symptoms.

Infections of the genitourinary tract

Favorable responses: Includes those designated as "good" or "satisfactory."

Good responses: Those in which *clinical* symptoms such as fever, back pain, dysuria, frequency, urgency, etc., are relieved promptly and pyuria cleared.

Satisfactory responses: Those in which there was relief or alleviation of some of the presenting symptoms and a reduction but no complete clearing of pyuria.

Poor responses: Those in which there was no significant effect on the symptoms and no appreciable change in pyuria.

Science for the world's well-being[®] (Pfizer logo) Since 1849 Pfizer Laboratories Division, Chas. Pfizer & Co., Inc. New York, New York 10017 p159X67 (c) 1967, Chas. Pfizer & Co., Inc. Printed in U.S.A. Issued -----

new from Pfizer research

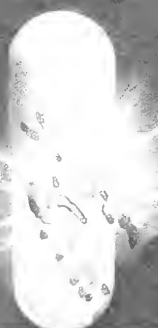
Vibramycin **doxycycline**

once-a-day
dosage

Vibramycin is the newest advance
in tetracycline research...
a unique homolog of oxytetracycline
and methacycline

In dosage and absorption

developed for efficiency



Vibramycin[®] **doxycycline**

an efficient oral broad-spectrum
antibiotic in terms of...

Serum concentrations of Vibramycin peak at a rate which approaches that of a tetracycline I.M. injection, indicating the great absorption of Vibramycin from the G.I. tract.

The lowest daily dose of any oral tetracycline.

Minimal dose-related G.I. side effects.

May be administered with meals or milk without significant loss of activity.

the
broad-spectrum
range of
Vibramycin
doxycycline
activity

Site of Infection	Indications	Pathogens (Susceptible Strains)
Ear Nose and Throat	Pharyngitis Tonsillitis Otitis media Sinusitis	Pneumococcus Beta-hemolytic streptococcus Staphylococcus H. influenzae
Lower Respiratory Tract	Single-lobe pneumonia Multilobe pneumonia Bronchopneumonia Bronchitis	Pneumococcus Streptococcus H. influenzae Klebsiella pneumoniae
Soft Tissue	Impetigo Furunculosis Cellulitis Abscess Infected wounds Paronychia	Staph. aureus Staph. albus Streptococcus E. coli Klebsiella-Aerobacter group
Genitourinary Tract	Pyelonephritis Cystitis Urethritis	Klebsiella-Aerobacter group E. coli Enterococcus Staphylococcus Streptococcus Neisseria gonorrhoeae

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include the following infections when caused by susceptible organisms:

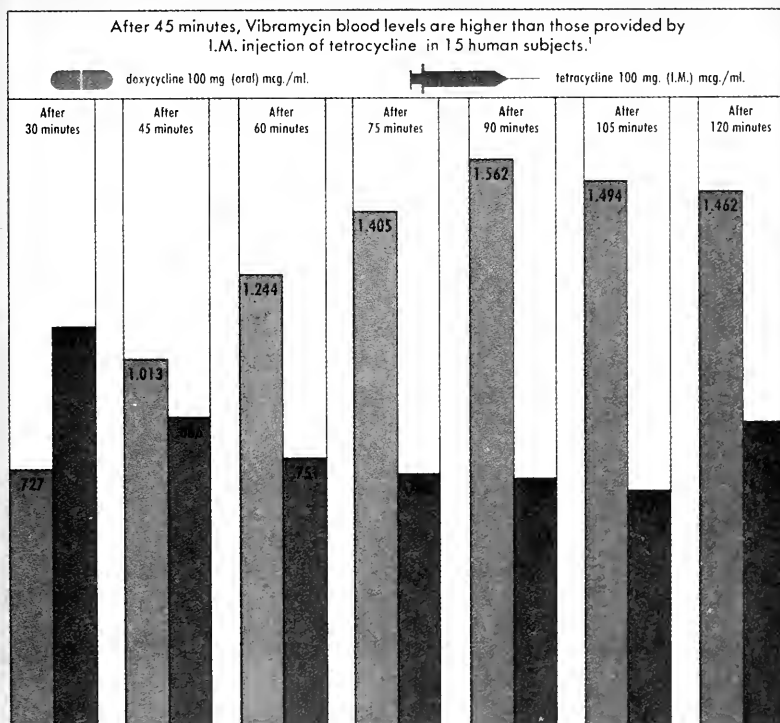
Site of Infection	Indications	Pathogens (Susceptible Strains)	
Other Areas	Ophthalmic infections	Gonococci Staphylococci H. influenzae	
	Gastrointestinal infections	E. histolytica Shigella	Salmonella Pathogenic E. coli
	Miscellaneous	Bacteroides Brucella* Listeria Mycoplasma pneumoniae (Eaton agent, PPLO) B. anthracis N. meningitidis Proteus *In combination with streptomycin	Donovania granulomatis Pasteurella Psittacosis virus Rickettsia H. pertussis C. welchii Treponema Pseudomonas

Vibramycin (doxycycline) may be useful in the treatment of acne vulgaris and acne conglobata.

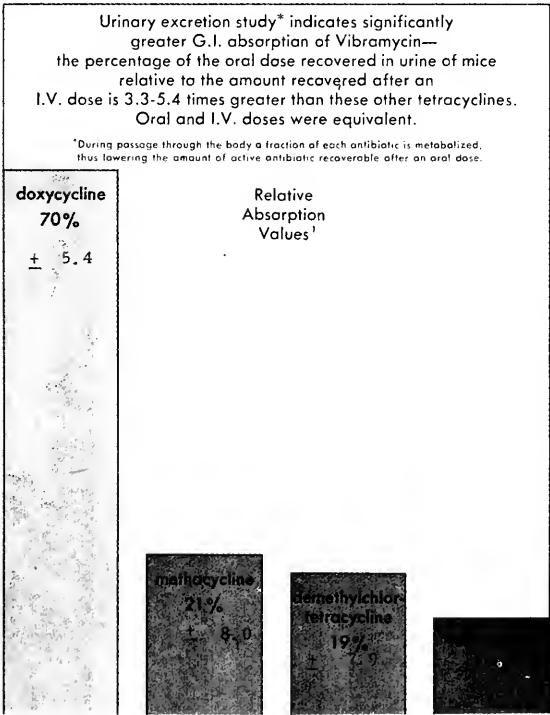
with
Vibramycin[®]
doxycycline

the lowest effective dose
the key:
efficient absorption

...as reflected in high blood levels
even in the critical first hour



...as demonstrated by
excretion studies in test animals



with
Vibramycin[®]
doxycycline

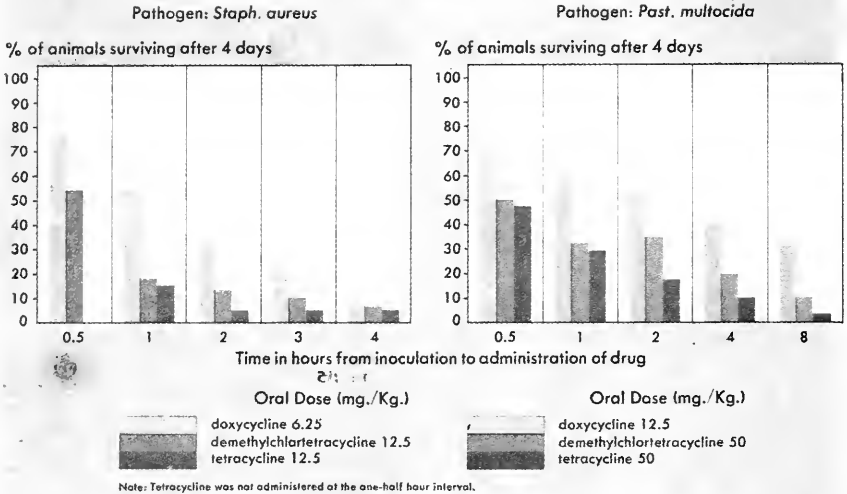
antibacterial effect demonstrated
in experimental animal studies²

Survival Time Studies in mice reflect rapid therapeutic concentrations of Vibramycin in the critical first hour of therapy.

the test:

1. Hundreds of mice were inoculated with an amount of bacteria that was known to be lethal without treatment (either *Staph. aureus* or *Past. multocida*). The two groups were kept separate.
2. At one-half hour after the lethal inoculation, four groups of 10 mice each were taken from each group and an antibiotic was orally administered. The antibiotics given and the dosage administered are listed below.
3. The same procedure was followed at 1 hour after the lethal inoculation and at intervals as indicated on the charts.
4. After a waiting period of 4 days, the animals surviving in each group were noted.
5. From the percentage of animals surviving at the various time intervals between the inoculation of the lethal quantity of bacteria and the oral administration of each antibiotic, the Survival Time₅₀ was calculated. (Survival Time₅₀ is that time at which, with the dosage administered, 50 per cent of the animals would have survived.)

the results:



The Survival Time Studies, while involving a limited number of organisms, resemble the clinical situation in that the infection is well established before antibiotics are administered.

the conclusion:

1. An important factor in protecting test animals is the rapidly attained, therapeutic concentrations of Vibramycin. (Mice infected with *Staph. aureus* are generally moribund about four hours after inoculation.)
2. Even at a fraction of the dosage of other tetracycline antibiotics tested, Vibramycin provided a greater and more persistent chemotherapeutic effect.

with
Vibramycin[®]
doxycycline

excellent
therapeutic results
in humans

over 90% clinical success rate³

Diagnosis Group	Clinical Response		Total	Per Cent Success
	Favorable	Poor		
Lower Respiratory Infections	172	11	183	94
Upper Respiratory Infections	143	11	154	93
Soft-Tissue Infections	133	8	141	94
Genitourinary Infections	57	19	76	75
Venereal (Gonococcal) Infections	175	14	189	93
Miscellaneous Infections	31	3	34	91
Totals	711	66	777	92

For criteria used in evaluating results of therapy, see end of brochure.

Summary of side effects
in 1,250 patients* treated with
Vibramycin[®]
doxycycline
not all of whom met the criteria
established for efficacy

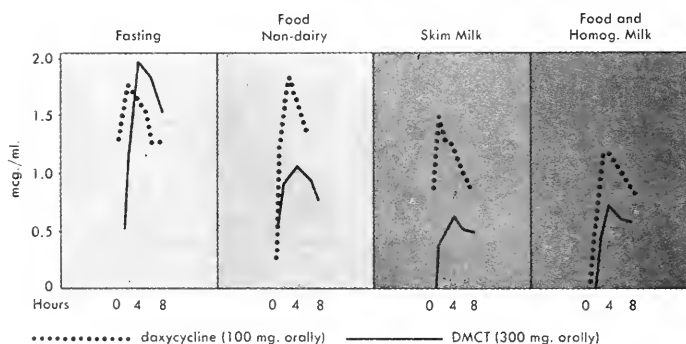
Side Effect	Number	Per Cent
Nausea	24	1.92
Vomiting	13	1.04
Diarrhea	8	0.64
Photosensitivity	7	0.56
Dermatitis	4	0.32
Flare-up of colitis	1	0.08
Glossitis	1	0.08
Stomatitis	2	0.16
Nail discoloration	1	0.08

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

with
Vibramycin[®]
doxycycline

absorption relatively
 unaffected in the presence
 of food or milk

Plasma levels of doxycycline and DMCT after oral ingestion of the drugs, fasting, and with foods in human subjects⁴

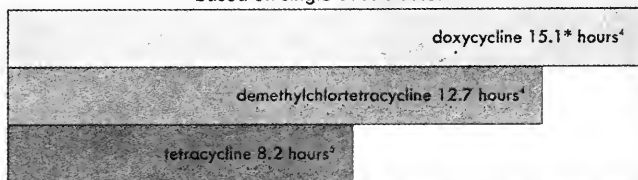


(Adopted from Rosenblatt, J. E., Barrett, J. E., Brodie, J. L. and Kirby, W. M. ⁴)

with
Vibramycin®
doxycycline

The lowest effective dose—
once a day after the first day
the key:
Long half-life.

Half-life of Vibramycin is significantly longer than that of other agents—
based on single dose studies.



*With multiple dosing, the cumulative half-life has been reported to be approximately 22 hours.⁶

Vibramycin owes its long half-life to slow renal clearance...
 $\frac{1}{2}$ that of DMCT, $\frac{1}{3}$ that of tetracycline.

Average Renal Clearance
(as a per cent of creatinine clearance)

doxycycline	12.0 ⁴
demethylchlortetracycline	26.8 ⁴
tetracycline	61.0 ⁵

with
Vibramycin[®]
doxycycline

Minimal untoward reactions in the lower G.I. tract as confirmed by the occurrence of only 8 cases of diarrhea among the 1,250 patients treated.³

the key:

efficient absorption

Since absorption of Vibramycin is high, a minimal quantity of antibiotic is left in the G.I. tract.

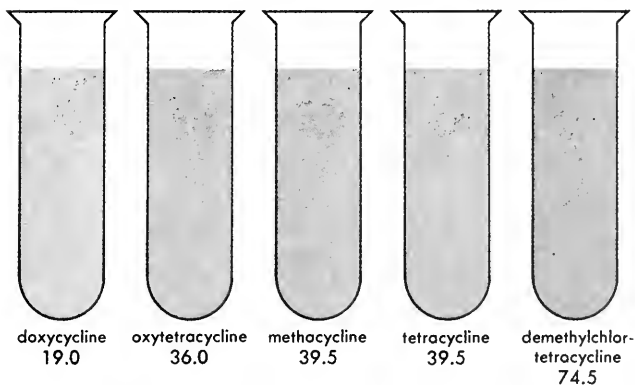
This would suggest the possibility of a lesser likelihood of monilial or bacterial overgrowth.

with
Vibramycin[™]
doxycycline

Lower degree of binding with calcium
than any other
tetracycline analog

Per cent of binding with calcium¹ with equal amounts of each antibiotic
(based on *in vitro* studies)

Binding was determined by shaking finely divided calcium phosphate in an aqueous solution of the antibiotic; per cent of antibiotic remaining in solution was measured by ultraviolet assay, and comparative binding was also demonstrated by relative fluorescence of the treated calcium phosphate.



From these *in vitro* data it may be postulated that...

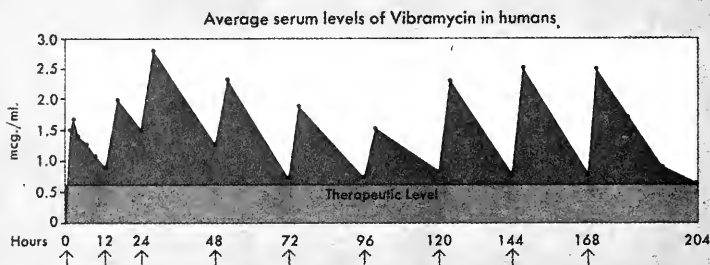
1. The absorption of Vibramycin will be relatively unaffected by food or milk.
2. Less Vibramycin may be deposited in bones or teeth.

with
Vibramycin®
doxycycline

Serum levels are therapeutic
around the clock'

the key:

Efficient absorption and long half-life



100 mg. of Vibramycin administered at hours indicated.
• Blood samples taken at hours indicated.

...and Vibramycin levels usually persist
24-36 hours after
cessation of therapy

after the first day of therapy...

the only one-dose-a-day broad-spectrum
antibiotic in oral form

Vibramycin
doxycycline once-a-day
dosage

In dosage and absorption

developed for efficiency



Vibramycin® Hyclate Capsules

doxycycline hyclate

Usual adult dosage			
Day 1	Day 2	Day 3	Subsequent Days
Two 50 mg. caps./b.i.d. (200 mg.)	Two 50 mg. caps./day (100 mg.)	Two 50 mg. caps./day (100 mg.)	Two 50 mg. caps./day (100 mg.)

In the management of more severe infections—100 mg. every 12 hours is recommended.

Vibramycin™ Hyclate Capsules contain doxycycline hyclate equivalent to 50 mg. doxycycline. Available in bottles of 50.

Vibramycin® Monohydrate for Oral Suspension

doxycycline monohydrate

Recommended dosage for children

First day of treatment—2 mg./lb. of body weight divided into two doses. Subsequent days—1 mg./lb. of body weight given as single daily dose or divided into two doses.

For more severe infections—up to 2 mg./lb. of body weight.

Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. (each teaspoonful), with a pleasant-tasting, raspberry flavor: 2 oz. bottles.



Criteria for evaluating clinical results:

Upper and lower respiratory infections

Soft tissue infections

Miscellaneous infections

Favorable responses:

Includes those designated as "good" or "satisfactory."

Good—patient showed definite favorable response to doxycycline therapy with prompt alleviation of symptoms.

Satisfactory—patient showed beneficial response, but the duration of symptoms was longer than might have been expected with a good response.

Poor responses:

Cases in which it was felt that there was no response, or a worsening of symptoms.

Infections of the genitourinary tract

Favorable responses:

Includes those designated as "good" or "satisfactory."

Good responses:

Those in which clinical symptoms such as fever, back pain, dysuria, frequency, urgency, etc., are relieved promptly and pyuria cleared.

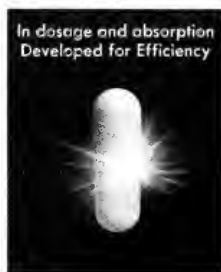
Satisfactory responses:

Those in which there was relief or alleviation of some of the presenting symptoms and a reduction but no complete clearing of pyuria.

Poor responses:

Those in which there was no significant effect on the symptoms and no appreciable change in pyuria.

References: 1. Research data on file, Pfizer Medical Department, Pfizer Laboratories. 2. English, A. R. and Lynch, J. E.: *Proc. Soc. Exp. Biol. Med.* 124:586, Feb., 1967. 3. Clinical data on file, Pfizer Medical Department, Pfizer Laboratories. Available to physicians on request. 4. Rosenblatt, J. E., Barrett, J. E., Bradie, J. L. and Kirby, W. M. M.: *Antimicrobial Agents and Chemotherapy*, 1966, Ann Arbor, American Society for Microbiology, 1967, pp. 134-141. 5. Kunia, C. M., Darnbush, A. C. and Finland, M.: *J. Clin. Invest.* 38:1950, Nov., 1959. 6. Migliardi, J. R. and Schoch von Wittenau, M.: presented at *Int. Cong. Chemother.*, Vienna, June 26-July 1, 1967.



Vibramycin® (doxycycline)

Description: Vibramycin (doxycycline) is a new broad spectrum antibiotic synthetically derived from methacycline, available as Vibramycin Monohydrate (doxycycline monohydrate) and Vibramycin Hyclate (doxycycline hydrochloride hemihydrate). The chemical designation of this light-yellow crystalline powder is 6-deoxy-5-oxo-tetracycline. Vibramycin (doxycycline) possesses the following useful properties not observed with previously available tetracyclines. Its greater absorption from the gastrointestinal tract and its capability for once-a-day maintenance dosage.

Actions: Vibramycin (doxycycline) is a broad-spectrum antibiotic and has been shown to be active *in vitro* against both gram-positive and gram-negative organisms. *In vivo* animal protection studies (PD₅₀) in mice and extensive clinical use in man have verified that Vibramycin (doxycycline) is a potent and effective antibiotic.

Vibramycin (doxycycline) differs from other tetracyclines by virtue of its greater absorption after oral administration and prolonged duration of *in vivo* antibacterial activity. Because of these factors, therapeutic effectiveness can be achieved by once-a-day maintenance dosage. Vibramycin (doxycycline) in therapeutic doses, given once daily, will produce serum activity usually persisting for 24 to 36 hours after discontinuation of therapy.

Vibramycin (doxycycline) has been administered to 60 normal volunteers for 70 days at a dose of 200 mg./day without evidence of increased toxicity.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline) is not notably influenced by the ingestion of food or milk, which do impair the absorption of certain other tetracyclines.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human use, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

Indications: Vibramycin (doxycycline) has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria.

Pneumonia: Single and multiple pneumonia and bronchopneumonia due to susceptible strains of *Pneumococcus*, *Streptococcus*, *Staphylococcus*, *H. influenzae*, and *Klebsiella pneumoniae*.

Other Respiratory Tract Infections: Pharyngitis, tonsillitis, otitis media, bronchitis and sinusitis caused by susceptible strains of β -hemolytic *Streptococcus*, *Staphylococcus*, *Pneumococcus*, and *H. influenzae*.

Genitourinary Tract Infections: Pyelonephritis, cystitis, urethritis caused by susceptible strains of the *Klebsiella*, *Aerobacter* group, *E. coli*, *Enterococcus*, *Staphylococcus*, *Streptococcus*, and *Neisseria gonorrhoeae*. Gonococcal urethritis in the male has been effectively treated by Vibramycin (doxycycline) at a dose of 100 mg. t.i.d. for a single day, but highest cure rates were achieved by a dose of 50 to 100 mg. b.i.d. for two to four days. Adult females with acute gonorrheal infections may require more extended therapy.

Soft-Tissue Infections: Impetigo, furunculosis, cellulitis, abscess, infected traumatic and postoperative wounds, paronychia caused by susceptible strains of *Staphylococcus aureus* and *albus*, *Streptococcus*, *E. coli*, and the *Klebsiella-Aerobacter* group. In the treatment of soft-tissue infections, indicated surgical procedures should be carried out in conjunction with Vibramycin (doxycycline) treatment.

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include infections caused by susceptible organisms, such as:

Ophthalmic Infections: Due to susceptible strains of *Gonococci*, *Staphylococci*, and *H. influenzae*.

Gastrointestinal Infections: Due to susceptible strains of such organisms as *E. histolytica*, pathogenic *E. coli*, and species of *Shigella* and *Salmonella*.

Miscellaneous: Other infections due to susceptible strains of *Bacteroides*, *Pasteurella*, *Brucella* (in combination with streptomycin), *Psittacosis*, *Listeria*, *Rickettsia*, *Mycoplasma pneumoniae* (Eaton agent, PPLO), *H. pertussis*, *B. anthracis*, *C. welchii*, *N. meningitidis*, *spirochetes* (Treponema), *Donaovicia granulomatis*, and *prostatitis* and *trigonitis* due to *Proteus* or *Pseudomonas*.

Vibramycin (doxycycline) may be useful in the treatment of acne vulgaris and acne conglobata.

Contraindications: This drug is contraindicated in individuals who have shown hypersensitivity to it.

Product Information

Warnings: If renal impairment exists, even usual doses may lead to excessive systemic accumulation of the drug and possible hepatic toxicity. Under such conditions, lower than usual doses are indicated and if treatment is prolonged, Vibramycin (doxycycline) serum level determinations may be advisable.

As with other tetracyclines, Vibramycin (doxycycline) may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines.

Though not observed in clinical studies to date and until evidence to the contrary develops, it should be anticipated that, like other tetracyclines, the use of Vibramycin (doxycycline) during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of teeth (yellowish-brownish). This tetracycline effect is more commonly associated with long term use of the drug, but has been known to occur with treatment of short duration.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving therapeutic doses of tetracyclines. Although the mechanism of this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight during the use of this drug. This reaction may also be produced by other tetracycline derivatives and is usually of the photoallergic type. Individuals with a history of photosensitivity reactions should be instructed to avoid exposure to direct sunlight while under treatment with tetracycline drugs, and treatment should be discontinued at first evidence of skin discomfort.

Precautions: The use of antibiotics may occasionally result in overgrowth of non-susceptible organisms. Constant observation of the patient is essential. If a resistant infection appears, the antibiotic should be discontinued and appropriate therapy instituted.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including dark field examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature, may occur but are rare. Glossitis, stomatitis, proctitis, anaphylaxis and discoloration of the nails may rarely occur during tetracycline therapy as with other antibiotics. If severe adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

Dosage: The usual dose of Vibramycin (doxycycline) is 200 mg on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg./lb. of body weight may be used. For children over 100 lbs. the usual adult dose should be used.

Therapy should be continued beyond the time that symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuation of Vibramycin (doxycycline). When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline), unlike certain other tetracyclines, is not markedly influenced by simultaneous ingestion of food or milk.

Simultaneous administration of aluminum hydroxide gel given with tetracycline antibiotics including Vibramycin (doxycycline) has been shown to decrease absorption.

Supply: Vibramycin Hyclate (doxycycline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline; bottles of 50. Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. [each teaspoonful], with a pleasant-tasting, raspberry flavor. 2 oz. bottles.



LABORATORIES DIVISION
New York, N.Y. 10017

CHAS. PFIZER & Co., INC.,
New York, N.Y., September 14, 1967.

Re Vibramycin.

ROBERT S. McCLEERY, M.D.,
*Director, Division of Medical Advertising, Bureau of Medicine,
Food and Drug Administration, Washington, D.C.*

DEAR DR. McCLEERY: Pursuant to our telephone discussion of September 13, 1967, we are submitting herein the visual aid for Vibramycin as clarified in accordance with our discussion. Also included herein is the dosage calculator which we feel is in line with our discussions concerning the visual aid.

In our telephone conversation you suggested that I indicate to you what course of action we would take concerning the previously submitted, but not now approved, promotional material. With regard to the original file card, which you have in draft copy and which we printed, you will recall that Mr. G. B. Stone stated that it would not be used by our Sales Representative in the form in which it is now printed. We have taken further steps to clarify certain statements in the file card in order to have it coincide with the information in the visual aid. Because of the need to leave something with the physician, under separate cover we are submitting another file card which consists of the package insert and dosage statement page which you have reviewed in our visual aid.

With regard to the compendium which we submitted, I have been requested to state that we would request your concurrence that we be permitted to use this compendium for the same period of time that we are now using the original visual aid. This compendium is primarily for use by the Professional Sales Representative for use in discussion with hospital representatives. It is not to be left with the physician until we have clarified the points in question and have received your approval for its use.

Sincerely yours,

J. P. ATERNO,
Manager, FDA Liaison Department.

new from Pfizer research

Vibramycin
doxycycline

VIBRAMYCIN (Doxycycline) Capsules

100 mg. and 50 mg. Capsules

a unique homolog of oxytetracycline
and methacycline

In dosage and absorption  developed for efficiency

Vibramycin[®] **doxycycline**

an efficient oral broad-spectrum
antibiotic in terms of...

Serum concentrations of Vibramycin peak at a rate which approaches that of a tetracycline I.M. injection, indicating the great absorption of Vibramycin from the G.I. tract.

Long half-life and slow urinary clearance of Vibramycin allow you to prescribe it on a one-dose-a-day basis after the first day.

FOR MORE SEVERE INFECTIONS, 100 MG. EVERY 12 HOURS IS RECOMMENDED.

The lowest daily dose of any oral tetracycline.

MINIMAL DOSE RELATED TO LOW G.I. SIDE EFFECT OBSERVED THIS FAR.

May be administered with meals or milk without significant loss of activity.

ANTIMICROBIAL SPECTRUM WHICH IS COMPATIBLE TO OTHER TETRACYCLINES.

the
broad-spectrum
range of

Vibramycin[®]
doxycycline

activity

VIBRAMYCIN HAS BEEN FOUND CLINICALLY EFFECTIVE IN THE TREATMENT OF A VARIETY OF INFECTIONS CAUSED BY SUSCEPTIBLE STRAINS OF GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA. *

Site of Infection	Indications	Pathogens (Susceptible Strains)
Ear Nose and Throat	Pharyngitis Tonsillitis Otitis media Sinusitis	Pneumococcus Beta-hemolytic streptococcus Staphylococcus H. influenzae
Lower Respiratory Tract	Single-lobe pneumonia Multilobe pneumonia Bronchopneumonia Bronchitis	Pneumococcus Streptococcus H. influenzae Klebsiella pneumoniae
Soft Tissue	Impetigo Furunculosis Cellulitis Abscess Infected wounds Paronychia	Staph. aureus Staph. albus Streptococcus E. coli Klebsiella-Aerobacter group
Genitourinary Tract	Pyelonephritis Cystitis Urethritis	Klebsiella-Aerobacter group E. coli Enterococcus Staphylococcus Streptococcus Neisseria gonorrhoeae

Since Vibromycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include the following infections when caused by susceptible organisms: *

Site of Infection	Indications	Pathogens (Susceptible Strains)	
Other Areas	Ophthalmic infections	Gonococci Staphylococci H. influenzae	
	Gastrointestinal infections	E. histolytica Shigella	Salmonella Pathogenic E. coli
	Miscellaneous	Bacteroides Brucella* Listeria Mycoplasma pneumoniae (Eaton agent, PPLO) B. anthracis N. meningitidis Proteus	Diplotheria granulomatis Pasteurella Psittacosis virus Rickettsia H. pertussis C. welchii Treponema Pseudomonas

ACNE VULGARIS AND ACNE ROSACEA

*In Combination with Streptomycin

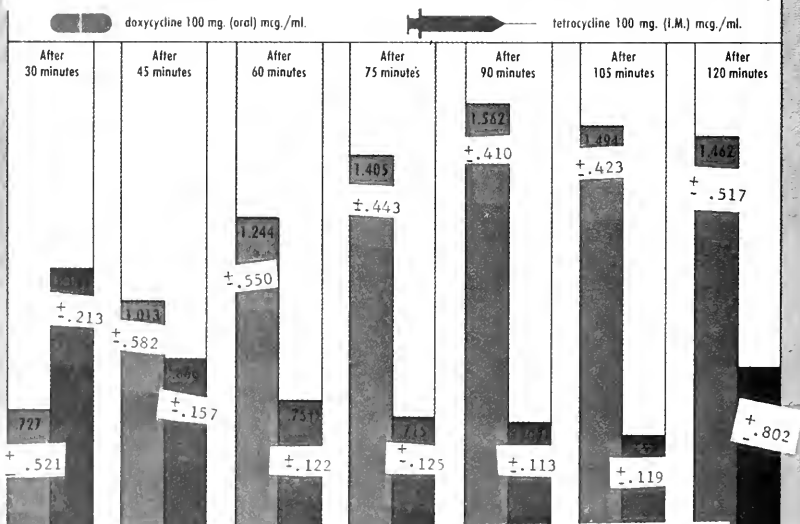
*BECAUSE NOT ALL STRAINS OF THE LISTED PATHOGENS ARE SUSCEPTIBLE, IT IS RECOMMENDED THAT ROUTINE CULTURE AND SUSCEPTIBILITY STUDIES BE PERFORMED.

with
Vibramycin[®]
doxycycline

the lowest effective dose
 the key:
efficient absorption

...as reflected IN EFFECTIVE blood levels
 even in the critical first hour

AFTER 60 MINUTES, VIBRAMYCIN BLOOD LEVELS ARE AS HIGH AS, OR HIGHER THAN, THOSE PROVIDED BY I.M. INJECTION OF TETRACYCLINE IN 15 HUMAN SUBJECTS¹



AFTER 60 MINUTES, THERE ARE STATISTICALLY SIGNIFICANT DIFFERENCES IN THE MEASURED SERUM LEVELS OF DOXYCYCLINE AND TETRACYCLINE. THE VARIANCE VALUES ACCOMPANYING THE MEASURED SERUM LEVELS REPRESENT \pm ONE STANDARD DEVIATION.

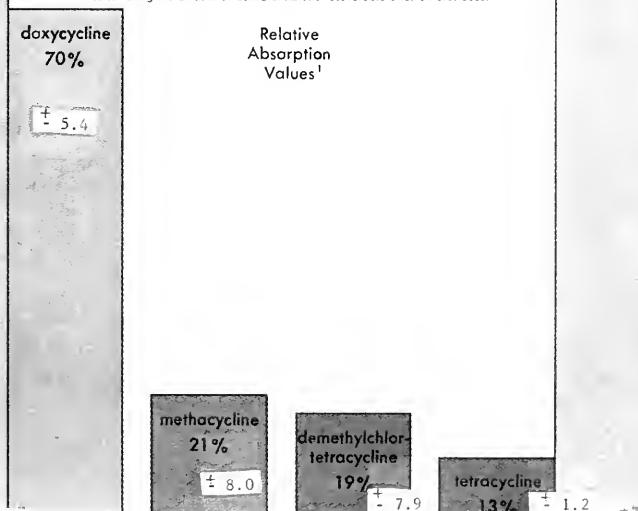
A SIMILAR COMPARISON IN DOSES SHOULD LESS PRONOUNCED DIFFERENCES BETWEEN THE DRUGS TESTED, BUT SUPPORTED THE CONCLUSION THAT, IN THE DOSE, 10% PERCENTAGE OF AN ORAL DOSE WHICH IS ABSORBED BY THE GASTROINTESTINAL TRACT IS PROBABLY TO 4 TIMES AS LARGE FOR DOXYCYCLINE AS FOR OTHER DRUGS TESTED.

(Bottom of page)

...as demonstrated by excretion studies in test animals

Urinary excretion study* indicates significantly greater G.I. absorption of Vibramycin—the percentage of the oral dose recovered in urine of 45 - 60% relative to the amount recovered after an I.V. dose is 3.3-5.4 times greater than these other tetracyclines. Oral and I.V. doses were equivalent.

*During passage through the body a fraction of each antibiotic is metabolized, thus lowering the amount of active antibiotic recoverable after an oral dose.



THE VARIANCE %'s ACCOMPANYING THE RELATIVE ABSORPTION VALUES REPRESENT ± ONE STANDARD DEVIATION.

with
Vibramycin®
doxycycline

antibacterial effect demonstrated
in experimental animal studies²

Survival Time Studies in mice reflect rapid therapeutic concentrations of Vibramycin in the critical first hour of therapy.

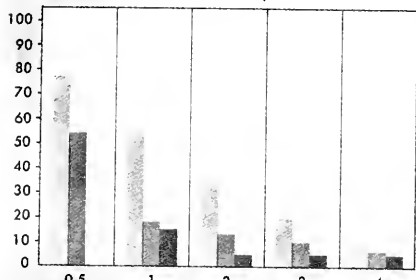
the test:

1. Hundreds of mice were inoculated with an amount of bacteria that was known to be lethal without treatment (either *Staph. aureus* or *Past. multocida*). The two groups were kept separate.
2. At one-half hour after the lethal inoculation, four groups of 10 mice each were taken from each group and an antibiotic was orally administered. The antibiotics given and the dosage administered are listed below.
3. The same procedure was followed at 1 hour after the lethal inoculation and at intervals as indicated on the charts.
4. After a waiting period of 4 days, the animals surviving in each group were noted.
5. From the percentage of animals surviving at the various time intervals between the inoculation of the lethal quantity of bacteria and the oral administration of each antibiotic, the Survival Time₅₀ was calculated. (Survival Time₅₀ is that time at which, with the dosage administered, 50 per cent of the animals would have survived.)

the results:

Pathogen: *Staph. aureus*

% of animals surviving after 4 days



Time in hours from inoculation to administration of drug
(EACH GROUP ANALYZED CONTAINED 10 ANIMALS)

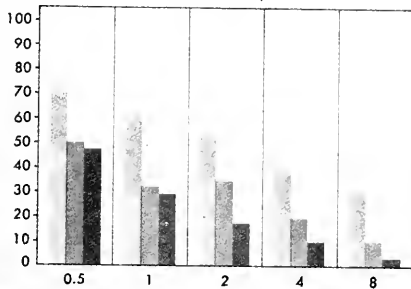
Oral Dose (mg./Kg.)



doxycycline 6.25
demethylchlortetracycline 12.5
tetracycline 12.5

Pathogen: *Past. multocida*

% of animals surviving after 4 days



Oral Dose (mg./Kg.)



doxycycline 12.5
demethylchlortetracycline 50
tetracycline 50

Note: Tetracycline was not administered at the one-half hour interval.

MICE INFECTED WITH *STAPH. AUREUS* ARE
GENERALLY MORIBUND WITHIN 4 HOURS

MICE INFECTED WITH *PAST. MULTOCIDA* ARE
GENERALLY MORIBUND WITHIN 24 HOURS.

The Survival Time Studies, while involving a limited number of organisms, resemble the clinical situation in that the infection is well established before antibiotics are administered.

the conclusion:

EVEN AT A FRACTION OF THE DOSAGE OF OTHER TETRACYCLINE ANTIBIOTICS TESTED, VIBRAMYCIN PROVIDED A GREATER AND MORE PERSISTENT CHEMOTHERAPEUTIC EFFECT.

(THE RESULTS OBTAINED CANNOT BE DIRECTLY COMPARED TO THE RESULTS OBTAINED WITH OTHER ANTIBIOTICS)

with
Vibramycin[®]
doxycycline

excellent
therapeutic results
in humans

over 90% clinical success rate³

OF 1250 PATIENTS TREATED WITH VIBRAMYCIN^R (doxycycline), THIS ANALYSIS OF THE CLINICAL SUCCESS RATE SPECIFICALLY INCLUDES THOSE CASES IN WHICH THE BACTERIOLOGIC ETIOLOGY WAS DETERMINED AND SENSITIVITY TESTING INDICATED ORGANISM SUSCEPTIBILITY. SENSITIVITY TESTING IS RECOGNIZED TO BE IMPORTANT FOR THE SELECTION OF THE MOST APPROPRIATE ANTIBIOTIC FOR A SPECIFIC PATIENT'S INFECTION.

DIAGNOSIS GROUP	CLINICAL RESPONSE		TOTAL	PER CENT SUCCESS
	FAVORABLE	POOR		
LOWER RESPIRATORY INFECTIONS	77	6	83	93
UPPER RESPIRATORY INFECTIONS	123	4	127	97
SOFT-TISSUE INFECTIONS	104	4	108	96
GENITOURINARY INFECTIONS	39	16	55	71
VENEREAL (GONOCOCCAL) INFECTIONS	66	2	68	97
MISCELLANEOUS INFECTIONS	12	1	13	92
TOTALS	421	33	454	

For criteria used in evaluating results of therapy, see end of brochure.

Summary of side effects
in 1,250 patients^a treated with
Vibramycin[®]
doxycycline
not all of whom met the criteria
established for efficacy

Side Effect	Number	Per Cent
Nausea	24	1.92
Vomiting	13	1.04
Diarrhea	8	0.64
Photosensitivity	7	0.56
Dermatitis	4	0.32
Flare-up of colitis	1	0.08
Glossitis	1	0.08
Stomatitis	2	0.16
Nail discoloration	1	0.08

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

with
Vibramycin
doxycycline

Minimal untoward reactions in the
lower G.I. tract as INDICATED
by the occurrence of only 8 cases
of diarrhea among the 1,250 patients treated.³

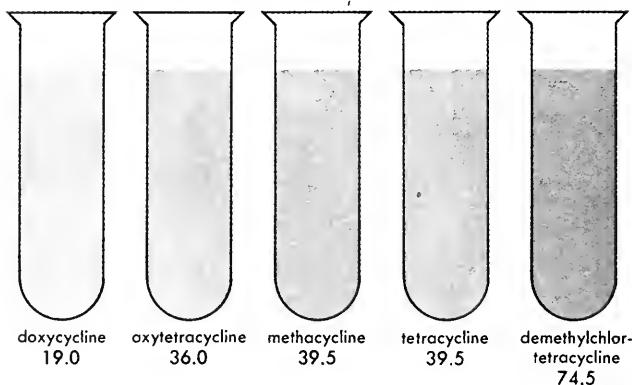
the key:
efficient absorption
Since absorption of Vibramycin is
high, a minimal quantity
of antibiotic is left in the G.I. tract.

with
Vibramycin[®]
doxycycline

Lower degree of IN VITRO BINDING WITH CALCIUM
than any other
tetracycline analog

Per cent of binding with calcium¹ with equal amounts of each antibiotic
(based on *in vitro* studies)

Binding was determined by shaking finely divided calcium phosphate in an aqueous solution of the antibiotic; per cent of antibiotic remaining in solution was measured by ultraviolet assay, and comparative binding was also demonstrated by relative fluorescence of the treated calcium phosphate.

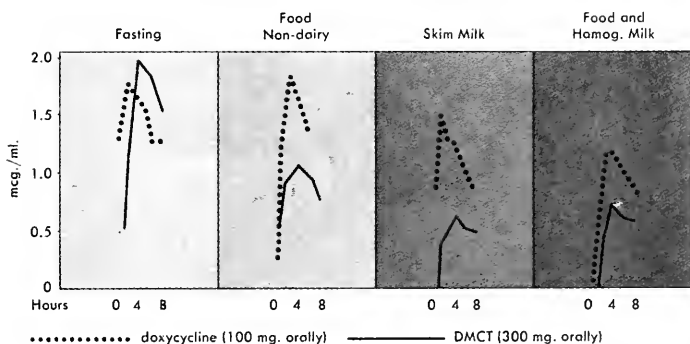


From these *in vitro* data it may be postulated that...
The absorption of Vibramycin will be relatively
unaffected by food or milk.

with
Vibramycin
doxycycline

absorption relatively
unaffected in the presence
of food or milk

Plasma levels of doxycycline and DMCT after oral ingestion of the drugs,
fasting, and with foods in 18 human subjects⁴



(Adapted from Rosenblatt, J. E., Barrett, J. E., Brodie, J. L. and Kirby, W. M. M.⁴)

with
Vibramycin[®]
doxycycline

The lowest effective dose—
 once a day after the first day
 the key:
Long half-life

Half-life of Vibramycin is significantly longer than that of other agents—
 based on single dose studies.

18 HUMAN SUBJECTS	doxycycline 15.1* hours ⁴
18 HUMAN SUBJECTS	demethylchlortetracycline 12.7 hours ⁴
4 HUMAN SUBJECTS	tetracycline 8.2 hours ⁴

THE HALF-LIFE VALUES BETWEEN DOXYCYCLINE AND TETRACYCLINE HAVE A MEAN DIFFERENCE OF ± 2.4 HR; STANDARD ERROR OF THE MEAN, 0.87 HR; $t \pm 2.76$, P-VALUE 0.02 AND ARE STATISTICALLY SIGNIFICANT.

⁴ 1/2 that of DMCI, 3/4 that of tetracycline.

lift up ↑

	Average Renal Clearance (as a per cent of creatinine clearance)	in human subjects
doxycycline	12.0 ± 2.5^4	(19 HUMAN SUBJECTS)
demethylchlortetracycline	26.6 ± 8.8^4	(19 HUMAN SUBJECTS)
tetracycline	62.0 ± 8.0^5	(4 HUMAN SUBJECTS)

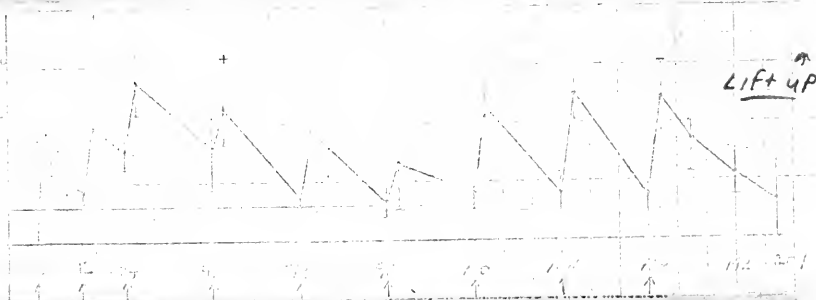
THE VARIANCE VALUES ACCOMPANYING THE AVERAGE RENAL CLEARANCE %'S REPRESENT \pm ONE STANDARD DEVIATION.

with
Vibramycin
doxycycline

Serum levels are MOST OFTEN THERAPEUTIC
 around the clock

the key:

Efficient absorption and long half-life



• Blood samples taken at hours indicated.

* THIS GRAPH REPRESENTS A COMPILATION OF
 THREE SEPARATE, BUT SIMILAR, STUDIES.

**...and Vibramycin levels usually persist
 24-36 hours after
 cessation of therapy**

+ THESE I-BARS GRAPHICALLY REPRESENT THE RANGE OF VARIANCE ABOUT A SERUM LEVEL
 POINT EQUIVALENT TO \pm ONE STANDARD DEVIATION.

after the first day of therapy...

the only one-dose-a-day broad-spectrum
antibiotic in oral form^{*}

Vibramycin
doxycycline

In dosage and absorption developed for efficiency



Vibramycin® Hyclate Capsules

doxycycline hyclate

Usual adult dosage			
Day 1	Day 2	Day 3	Subsequent Days
Two 50 mg. caps./b.i.d. (200 mg.)	Two 50 mg. caps./day (100 mg.)	Two 50 mg. caps./day (100 mg.)	Two 50 mg. caps./day (100 mg.)

In the management of more severe infections—100 mg. every 12 hours is recommended.

Vibramycin® Hyclate Capsules contain doxycycline hyclate equivalent to 50 mg. doxycycline. Available in bottles of 50.

Vibramycin® Monohydrate for Oral Suspension

doxycycline monohydrate

Recommended dosage for children

First day of treatment—2 mg./lb. of body weight divided into two doses. Subsequent days—1 mg./lb. of body weight given as single daily dose or divided into two doses.

For more severe infections—up to 2 mg./lb. of body weight. Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. (each teaspoonful), with a pleasant-tasting, raspberry flavor: 2 oz. bottles.



Criteria for evaluating clinical results:

Upper and lower respiratory infections

Soft tissue infections

Miscellaneous infections

Favorable responses:

Includes those designated as "good" or "satisfactory."

Good—patient showed definite favorable response to doxycycline therapy with prompt alleviation of symptoms.

Satisfactory—patient showed beneficial response, but the duration of symptoms was longer than might have been expected with a good response.

Poor responses:

Cases in which it was felt that there was no response, or a worsening of symptoms.

Infections of the genitourinary tract

Favorable responses:

Includes those designated as "good" or "satisfactory."

Good responses:

Those in which clinical symptoms such as fever, back pain, dysuria, frequency, urgency, etc., are relieved promptly and pyuria cleared.

Satisfactory responses:

Those in which there was relief or alleviation of some of the presenting symptoms and a reduction but no complete clearing of pyuria.

Poor responses:

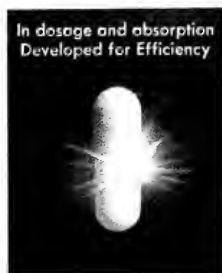
Those in which there was no significant effect on the symptoms and no appreciable change in pyuria.

FOR MORE SEVERE INFECTIONS, 100 MG. EVERY 12 HOURS IS RECOMMENDED.

MINIMAL DOSE RELATED LOWER G.I. SIDE EFFECTS OBSERVED THUS FAR.

ANTIMICROBIAL SPECTRUM WHICH IS COMPARABLE TO OTHER TETRACYCLINES.

References: 1. Research data on file, Pfizer Medical Department, Pfizer Laboratories. 2. English, A. R. and Lynch, J. E.: *Proc. Soc. Exp. Biol. Med.* 124:586, Feb., 1967. 3. Clinical data on file, Pfizer Medical Department, Pfizer Laboratories. Available to physicians on request. 4. Rosenblatt, J. E., Barrett, J. E., Bradie, J. L. and Kirby, W. M. M.: *Antimicrobial Agents and Chemotherapy*, 1966, Ann Arbor, American Society for Microbiology, 1967, pp. 134-141. 5. Kunin, C. M., Darnbush, A. C. and Finlund, M.: *J Clin. Invest.* 38:1950, Nov., 1959. 6. Migliardi, J. R. and Schach van Wiltencou, M., presented at Int. Cong. Chemother., Vienna, June 26-July 1, 1967.



Vibramycin® (doxycycline)

Product Information

Description: Vibramycin (doxycycline) is a new broad-spectrum antibiotic synthetically derived from methacycline, available as Vibramycin Monohydrate (doxycycline monohydrate) and Vibramycin Hyclate (doxycycline hydrochloride hemihydrate). The chemical designation of this light-yellow crystalline powder is 6-6-deoxy-3-oxy-tetracycline. Vibramycin (doxycycline) possesses the following useful properties not observed with previously available tetracyclines: its greater absorption from the gastrointestinal tract and its capability for once-a-day maintenance dosage.

Actions: Vibramycin (doxycycline) is a broad-spectrum antibiotic and has been shown to be active *in vitro* against both gram-positive and gram-negative organisms. *In vivo* animal protection studies (P03a) in mice and extensive clinical use in man have verified that Vibramycin (doxycycline) is a potent and effective antibiotic.

Vibramycin (doxycycline) differs from other tetracyclines by virtue of its greater absorption after oral administration and prolonged duration of *in vivo* antibacterial activity. Because of these factors, therapeutic effectiveness can be achieved by once-a-day maintenance dosage. Vibramycin (doxycycline) in therapeutic doses, given once daily, will produce serum activity usually persisting for 24 to 36 hours after discontinuation of therapy.

Vibramycin (doxycycline) has been administered to 60 normal volunteers for 70 days at a dose of 200 mg./day without evidence of increased toxicity.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline) is not notably influenced by the ingestion of food or milk, which do impair the absorption of certain other tetracyclines.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

Indications: Vibramycin (doxycycline) has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria.

Pneumonia: Single and multiple pneumonia and bronchopneumonia due to susceptible strains of *Pneumococcus*, *Streptococcus*, *Staphylococcus*, *H. influenzae*, and *Klebsiella pneumoniae*.

Other Respiratory Tract Infections: Pharyngitis, tonsillitis, otitis media, bronchitis and sinusitis caused by susceptible strains of β -hemolytic *Streptococcus*, *Staphylococcus*, *Pneumococcus*, and *H. influenzae*.

Genitourinary Tract Infections: Pyelonephritis, cystitis, urethritis caused by susceptible strains of the *Klebsiella-Aerobacter* group, *E. coli*, *Enterococcus*, *Staphylococcus*, *Streptococcus*, and *Neisseria gonorrhoeae*. Gonococcal urethritis in the male has been effectively treated by Vibramycin (doxycycline) at a dose of 100 mg. t.i.d. for a single day, but highest cure rates were achieved by a dose of 50 to 100 mg. b.i.d. for two to four days. Adult females with acute gonorrheal infections may require more extended therapy.

Soft-Tissue Infections: Impetigo, furunculosis, cellulitis, abscess, infected traumatic and postoperative wounds, paronychia caused by susceptible strains of *Staphylococcus aureus* and *albus*, *Streptococcus*, *E. coli*, and the *Klebsiella-Aerobacter* group. In the treatment of soft-tissue infections, indicated surgical procedures should be carried out in conjunction with Vibramycin (doxycycline) treatment.

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include infections caused by susceptible organisms, such as:

Ophthalmic Infections: Due to susceptible strains of *Gonococci*, *Staphylococci*, and *H. influenzae*.

Gastrointestinal Infections: Due to susceptible strains of such organisms as *E. histolytica*, pathogenic *E. coli*, and species of *Shigella* and *Salmonella*. Miscellaneous: Other infections due to susceptible strains of *Bacteroides*, *Pasteurella*, *Brucella* (in combination with streptomycin), *Psittacosis*, *Listeria*, *Rickettsia*, *Mycoplasma pneumoniae* (Eaton agent, PPL0), *H. pertussis*, *B. anthracis*, *C. welchii*, *N. meningitidis*, spirochetes (Treponema), *Gonorrhea granulomatosa*, and prostaticitis and trigonitis due to *Proteus* or *Pseudomonas*.

Vibramycin (doxycycline) may be useful in the treatment of acne vulgaris and acne conglobata.

Contraindications: This drug is contraindicated in individuals who have shown hypersensitivity to it.

Warnings: If renal impairment exists, even usual doses may lead to excessive systemic accumulation of the drug and possible hepatic toxicity. Under such conditions, lower than usual doses are indicated and if treatment is prolonged, Vibramycin (doxycycline) serum level determinations may be advisable.

As with other tetracyclines, Vibramycin (doxycycline) may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines.

Though not observed in clinical studies to date and until evidence to the contrary develops, it should be anticipated that, like other tetracyclines, the use of Vibramycin (doxycycline) during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of teeth (yellow-gray-brownish). This tetracycline effect is more commonly associated with long-term use of the drug, but has been known to occur with treatment of short duration.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving therapeutic doses of tetracyclines. Although the mechanism of this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight during the use of this drug. This reaction may also be produced by other tetracycline derivatives and is usually of the photosensitive type. Individuals with a history of photosensitivity reactions should be instructed to avoid exposure to direct sunlight while under treatment with tetracycline drugs, and treatment should be discontinued at first evidence of skin discomfort.

Precautions: The use of antibiotics may occasionally result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If a resistant infection appears, the antibiotic should be discontinued and appropriate therapy instituted.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including dark-field examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature, may occur but are rare. Glossitis, stomatitis, proctitis, onycholysis and discoloration of the nails may rarely occur during therapeutic therapy as with other antibiotics. If severe adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

Dosage: The usual dose of Vibramycin (doxycycline) is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg./lb. of body weight may be used. For children over 100 lbs. the usual adult dose should be used.

Therapy should be continued beyond the time that symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuation of Vibramycin (doxycycline). When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline), unlike certain other tetracyclines, is not markedly influenced by simultaneous ingestion of food or milk.

Simultaneous administration of aluminum hydroxide gel given with tetracycline antibiotics including Vibramycin (doxycycline) has been shown to decrease absorption.

Supply: Vibramycin Hyclate (doxycycline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline; bottles of 50 Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. (each teaspoonful), with a pleasant-tasting, raspberry flavor. 2 oz. bottles.

Pfizer LABORATORIES DIVISION
New York, N.Y. 10017

CHAS. PFIZER & CO., INC.,
New York, N.Y., October 6, 1967.

Re Vibramycin—§ 148z. 3 and § 148z. 4.

ROBERT S. MCCLEERY, M.D.,
*Director, Division of Medical Advertising, Bureau of Medicine, Food and Drug
Administration, Washington, D.C.*

DEAR DR. MCCLEERY: We refer you to your meetings with Mr. Aterno and Dr. Trout on September 5 and September 6, 1967 in regard to Vibramycin.

As a result of these meetings Dr. Ley gave us permission to use the existing Vibramycin visual aid and compendium for a period of one month from the date of approval (September 14, 1967) and we were then to replace that visual with the new revised visual aid.

During the coming week of October 9, 1967 the new visual aids will be sent to our sales force. Upon receipt of the revised visual aid the detailman will return his copy to his District Manager and will sign a return sheet. The visual aid, along with the compendium, will then be returned to the company where they will be destroyed.

Sincerely yours,

M. G. ADAIR,
FDA Liaison Department.

new from Pfizer research

Vibramycin ***doxycycline***

Vibramycin is a new member of
the tetracycline family
a unique homolog of oxytetracycline
and methacycline

In dosage and absorption developed for efficiency



Vibramycin[®] **doxycycline**

an efficient oral broad-spectrum
antibiotic in terms of...

Serum concentrations of Vibramycin peak at a rate which approaches that of a tetracycline I.M. injection, indicating the great absorption of Vibramycin from the G.I. tract.

Long half-life and slow urinary clearance of Vibramycin allow you to prescribe it on a one-dose-a-day basis after the first day.

For more severe infections, 100 mg. every 12 hours is recommended.

Minimal dose-related lower G.I. side effects observed thus far.

May be administered with meals or milk without significant loss of activity.

Antimicrobial spectrum which is comparable to other tetracyclines.

the
broad-spectrum
range of

Vibramycin[®]
doxycycline

activity

Vibramycin has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria.*

Site of Infection	Indications	Pathogens (Susceptible Strains)
Ear Nose and Throat	Pharyngitis Tonsillitis Otitis media Sinusitis	Pneumococcus Beta-hemolytic streptococcus Staphylococcus H. influenzae
Lower Respiratory Tract	Single-lobe pneumonia Multilobe pneumonia Bronchopneumonia Bronchitis	Pneumococcus Streptococcus H. influenzae Klebsiella pneumoniae
Soft Tissue	Impetigo Furunculosis Cellulitis Abscess Infected wounds Paronychia	Staph. aureus Staph. albus Streptococcus E. coli Klebsiella-Aerobacter group
Genitourinary Tract	Pyelonephritis Cystitis Urethritis	Klebsiella-Aerobacter group E. coli Enterococcus Staphylococcus Streptococcus Neisseria gonorrhoeae

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include the following infections when caused by susceptible organisms:*

Site of Infection	Indications	Pathogens (Susceptible Strains)
Other Areas	Ophthalmic infections	Gonococci Staphylococci H. influenzae
	Gastrointestinal infections	E. histolytica Shigella
		Salmonella Pathogenic E. coli
	Miscellaneous	Bacteroides Brucella Listeria Mycoplasma pneumoniae (Eaton agent, PPLO) B. anthracis N. meningitidis Proteus
		Donaevia granulomatis Pasteurella Psittacosis virus Rickettsia H. pertussis C. welchii Treponema Pseudomonas
	Acne vulgaris and acne conglobata	
	*In combination with streptomycin	

*Because not all strains of the listed pathogens are susceptible, it is recommended that routine culture and susceptibility studies be performed.

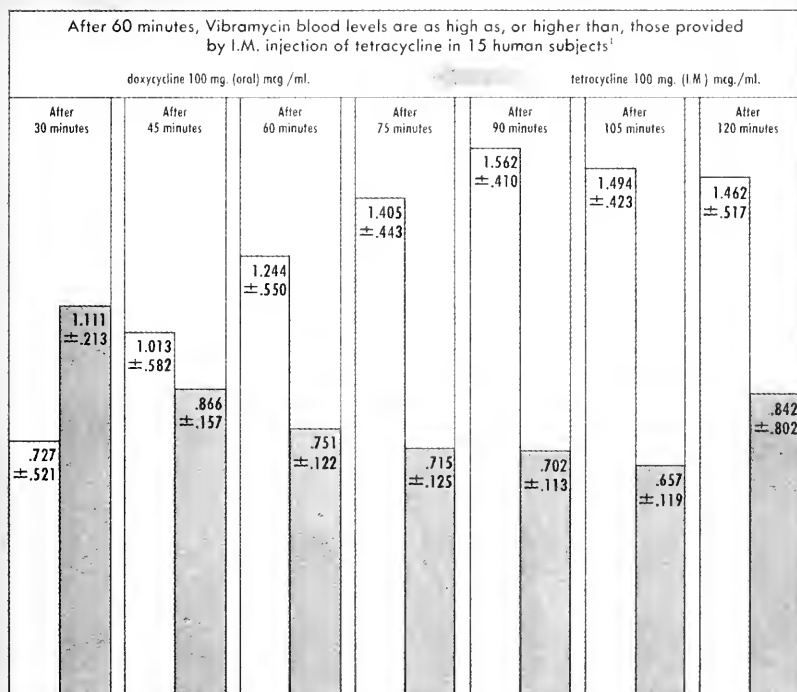
with
Vibramycin[®]
doxycycline

the lowest effective dose

the key:

efficient absorption

...as reflected in effective blood levels
 even in the critical first hour

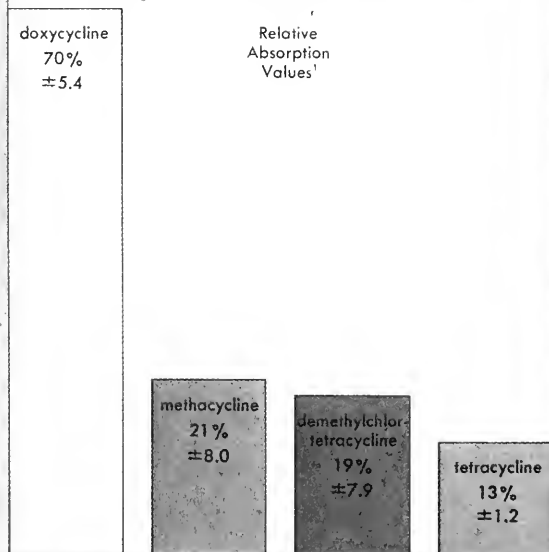


After 60 minutes, there are statistically significant differences in the measured serum levels of doxycycline and tetracycline. The variance values accompanying the measured serum levels represent \pm one standard deviation.

...as demonstrated by excretion studies in test animals

Urinary excretion study* indicates significantly greater G.I. absorption of Vibramycin—the percentage of the oral dose recovered in urine of 45-60 mice relative to the amount recovered after an I.V. dose is 3.3-5.4 times greater than these other tetracyclines. Oral and I.V. doses were equivalent.

*During passage through the body a fraction of each antibiotic is metabolized, thus lowering the amount of active antibiotic recoverable after an oral dose.



The variance %'s accompanying the relative absorption values represent \pm one standard deviation.

A similar comparison in dogs showed less pronounced differences between the drugs tested, but supported the conclusion that, in the dog, the percentage of an oral dose which is absorbed by the gastrointestinal tract is from 2 to 4 times as large for doxycycline as for other drugs tested.

with
Vibramycin[®]
doxycycline

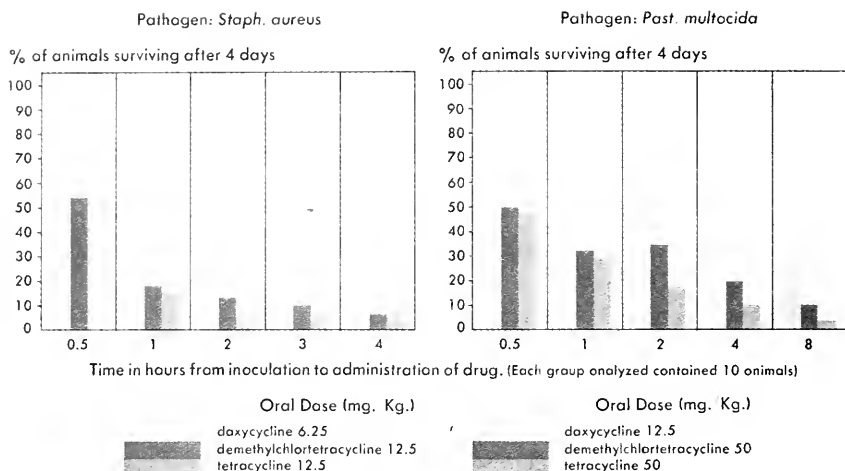
antibacterial effect demonstrated
in experimental animal studies²

Survival Time Studies in mice reflect rapid therapeutic concentrations of Vibramycin in the critical first hour of therapy.

the test:

1. Hundreds of mice were inoculated with an amount of bacteria that was known to be lethal without treatment (either Staph. aureus or Past. multocida). The two groups were kept separate.
2. At one-half hour after the lethal inoculation, four groups of 10 mice each were taken from each group and an antibiotic was orally administered. The antibiotics given and the dosage administered are listed below.
3. The same procedure was followed at 1 hour after the lethal inoculation and at intervals as indicated on the charts.
4. After a waiting period of 4 days, the animals surviving in each group were noted.
5. From the percentage of animals surviving at the various time intervals between the inoculation of the lethal quantity of bacteria and the oral administration of each antibiotic, the Survival Time₅₀ was calculated. (Survival Time₅₀ is that time at which, with the dosage administered, 50 per cent of the animals would have survived.)

the results:



Note. Tetracycline was not administered at the one-half hour interval.

Mice infected with *Staph. aureus* are generally moribund within 4 hours.

Mice infected with *Past. multocida* are generally moribund within 24 hours.

The Survival Time Studies, while involving a limited number of organisms, resemble the clinical situation in that the infection is well established before antibiotics are administered.

the conclusion:

Even at a fraction of the dosage of other tetracycline antibiotics tested, Vibramycin provided a greater and more persistent chemotherapeutic effect.

The results obtained cannot be directly extrapolated to the clinical situation.

with
Vibramycin[®]
doxycycline

excellent
therapeutic results
in humans

over 90% clinical success rate³

Of 1,250 patients treated with Vibramycin® (doxycycline), this analysis of the clinical success rate includes those cases in which the bacteriologic etiology was determined and sensitivity testing indicated organism susceptibility. Sensitivity testing is recognized to be important for the selection of the most appropriate antibiotic for a specific patient's infection.

Diagnosis Group	Clinical Response		Total	Per Cent Success
	Favorable	Poor		
Lower Respiratory Infections	77	6	83	93
Upper Respiratory Infections	123	4	127	97
Soft-Tissue Infections	104	4	108	96
Genitourinary Infections	39	16	55	71
Venereal (Gonococcal) Infections	66	2	68	97
Miscellaneous Infections	12	1	13	92
Totals	421	33	454	

For criteria used in evaluating results of therapy, see end of brochure.

Summary of side effects
in 1,250 patients³ treated with
Vibramycin
doxycycline
not all of whom met the criteria
established for efficacy

Side Effect	Number	Per Cent
Nausea	24	1.92
Vomiting	13	1.04
Diarrhea	8	0.64
Photosensitivity	7	0.56
Dermatitis	4	0.32
Flare-up of colitis	1	0.08
Glossitis	1	0.08
Stomatitis	2	0.16
Nail discoloration	1	0.08

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

with
Vibramycin
doxycycline

Minimal untoward reactions in the lower G.I. tract as indicated by the occurrence of only 8 cases of diarrhea among the 1,250 patients treated.³

the key:
efficient absorption

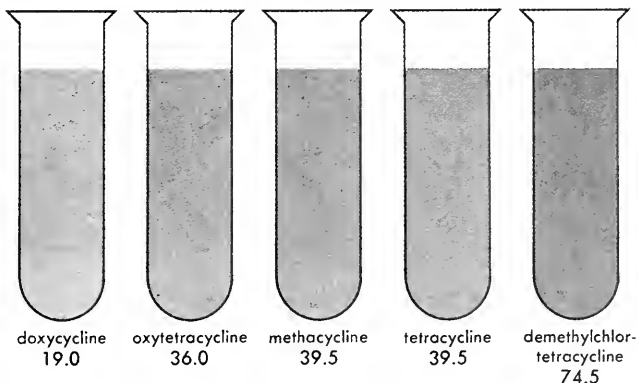
Since absorption of Vibramycin is high, a minimal quantity of antibiotic is left in the G.I. tract.

with
Vibramycin
doxycycline

Lower degree of *in vitro* binding with calcium
than any other
tetracycline analog

Per cent of binding with calcium¹ with equal amounts of each antibiotic
(based on *in vitro* studies)

Binding was determined by shaking finely divided calcium phosphate in an aqueous solution of the antibiotic; per cent of antibiotic remaining in solution was measured by ultraviolet assay, and comparative binding was also demonstrated by relative fluorescence of the treated calcium phosphate.

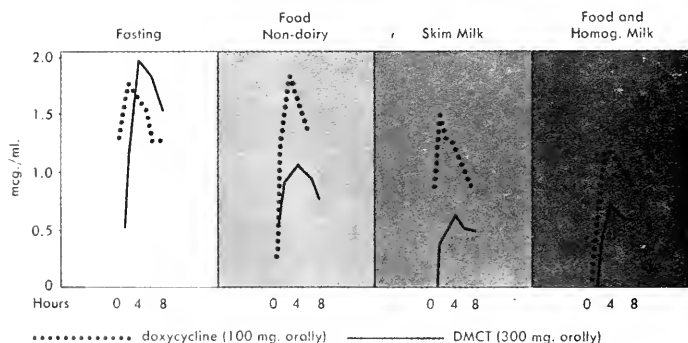


From these *in vitro* data it may be postulated that...
The absorption of Vibramycin will be relatively
unaffected by food or milk.

with
Vibramycin
 doxycycline

absorption relatively
 unaffected in the presence
 of food or milk

Plasma levels of doxycycline and DMCT after oral ingestion of the drugs,
 fasting, and with foods in 18 human subjects⁴



(Adapted from Rosenblatt, J. E., Barrett, J. E., Brodie, J. L. and Kirby, W. M. M.⁴)

with
Vibramycin
doxycycline

The lowest effective dose—
 once a day after the first day
 the key:
Long half-life

Half-life of Vibramycin is significantly longer than that of other agents—
 based on single-dose studies.

18 human subjects	doxycycline 15.1* hours ⁴
18 human subjects	demethylchlortetracycline 12.7 hours ⁴
4 human subjects	tetracycline 8.2 hours ⁵

The half-life values between doxycycline and DMCT have a mean difference of ± 2.4 hr; standard error of the mean, 0.87 hr; $t \pm 2.76$, P-value 0.02 and are statistically significant.

Vibramycin owes its long half-life to slow renal clearance...
 $\frac{1}{2}$ that of DMCT, $\frac{1}{3}$ that of tetracycline.

Average Renal Clearance in Human Subjects
 (as a per cent of creatinine clearance)

doxycycline	12.0 ± 2.5	(19 human subjects) ⁴
demethylchlortetracycline	26.6 ± 8.8	(19 human subjects) ⁴
tetracycline	62.0 ± 8.0	(4 human subjects) ⁵

The variance values accompanying the average renal clearance %'s
 represent \pm one standard deviation.

U.S. 2000

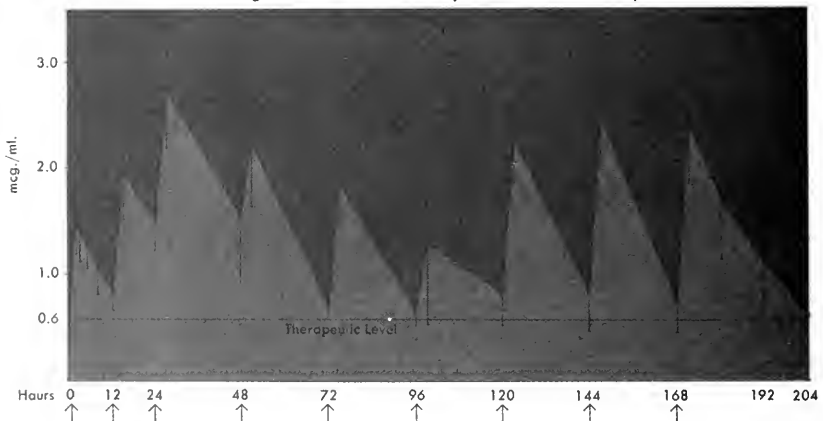
with
Vibramycin[®]
doxycycline

Serum levels are most often therapeutic
 around the clock[†]

the key:

Efficient absorption and long half-life

Average serum levels of Vibramycin in 6-23 human subjects*



100 mg. of Vibramycin administered at hours indicated.

* Blood samples taken at hours indicated.

*This graph represents a compilation of three separate, but similar, studies. †These I-bars graphically represent the range of variance about a serum level point equivalent to \pm one standard deviation.

...and Vibramycin levels usually persist
 24-36 hours after cessation of therapy

after the first day of therapy...

the only one-dose-a-day broad-spectrum
antibiotic in oral form*

Vibramycin
doxycycline

In dosage and absorption... developed for efficiency



*In the management of more severe infections, 100 mg. every 12 hours is recommended.

Vibramycin® Hyclate Capsules

doxycycline hyclate

Usual adult dosage			
Day 1	Day 2	Day 3	Subsequent Days
Two 50 mg. caps./b.i.d. (200 mg.)	Two 50 mg. caps./day (100 mg.)	Two 50 mg. caps./day (100 mg.)	Two 50 mg. caps./day (100 mg.)

In the management of more severe infections—100 mg. every 12 hours is recommended.

Vibramycin® Hyclate Capsules contain doxycycline hyclate equivalent to 50 mg. doxycycline. Available in bottles of 50.

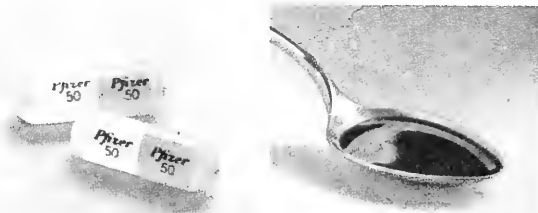
Vibramycin® Monohydrate for Oral Suspension

doxycycline monohydrate

Recommended dosage for children

First day of treatment—2 mg./lb. of body weight divided into two doses. Subsequent days—1 mg./lb. of body weight given as single daily dose or divided into two doses.

For more severe infections—up to 2 mg./lb. of body weight. Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. (each teaspoonful), with a pleasant-tasting, raspberry flavor: 2 oz. bottles.



Criteria for evaluating clinical results:

Upper and lower respiratory infections

Soft tissue infections

Miscellaneous infections

Favorable responses:

Includes those designated as "good" or "satisfactory."

Good—patient showed definite favorable response to doxycycline therapy with prompt alleviation of symptoms.

Satisfactory—patient showed beneficial response, but the duration of symptoms was longer than might have been expected with a good response.

Poor responses:

Cases in which it was felt that there was no response, or a worsening of symptoms.

Infections of the genitourinary tract

Favorable responses:

Includes those designated as "good" or "satisfactory."

Good responses:

Those in which clinical symptoms such as fever, back pain, dysuria, frequency, urgency, etc., are relieved promptly and pyuria cleared.

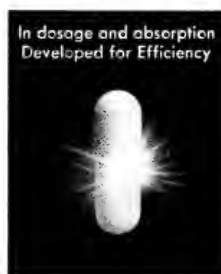
Satisfactory responses:

Those in which there was relief or alleviation of some of the presenting symptoms and a reduction but no complete clearing of pyuria.

Poor responses:

Those in which there was no significant effect on the symptoms and no appreciable change in pyuria.

References: 1. Research data on file, Pfizer Medical Department, Pfizer Laboratories. 2. English, A. R. and Lynch, J. E.: *Proc. Soc. Exp. Biol. Med.* 124:586, Feb., 1967. 3. Clinical data on file, Pfizer Medical Department, Pfizer Laboratories. Available to physicians on request. 4. Rosenblatt, J. E., Barrett, J. E., Brodie, J. L. and Kirby, W. M. M.: *Antimicrobial Agents and Chemotherapy*, 1966, Ann Arbor, American Society for Microbiology, 1967, pp. 134-141. 5. Kunin, C. M., Dornbush, A. C. and Finland, M.: *J. Clin. Invest.* 38:1950, Nov., 1959. 6. Migliardi, J. R. and Schach von Wittenau, M., presented at Int. Cong. Chemother., Vienna, June 26-July 1, 1967.



Vibramycin® (doxycycline)

Product Information

Description: Vibramycin (doxycycline) is a new broad-spectrum antibiotic synthetically derived from tetracycline, available as Vibramycin Monohydrate (doxycycline monohydrate) and Vibramycin Hyclate (doxycycline hydrochloride hemihydrate). The chemical designation of this light-yellow crystalline powder is 4-deoxy-5-oxo-tetracycline. Vibramycin (doxycycline) possesses the following useful properties not observed with previously available tetracyclines: its greater absorption from the gastrointestinal tract and its capability for once-a-day maintenance dosage.

Actions: Vibramycin (doxycycline) is a broad-spectrum antibiotic and has been shown to be active *in vitro* against both gram-positive and gram-negative organisms. In vivo animal protection studies (PD₅₀) in mice and extensive clinical use in man have verified that Vibramycin (doxycycline) is a potent and effective antibiotic.

Vibramycin (doxycycline) differs from other tetracyclines by virtue of its greater absorption after oral administration and prolonged duration of *in vivo* antibacterial activity. Because of these factors, therapeutic effectiveness can be achieved by once-a-day maintenance dosage. Vibramycin (doxycycline) in therapeutic doses, given once daily, will produce serum activity usually persisting for 24 to 36 hours after discontinuation of therapy.

Vibramycin (doxycycline) has been administered to 60 normal volunteers for 70 days at a dose of 200 mg/day without evidence of increased toxicity.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline) is not notably influenced by the ingestion of food or milk, which do impair the absorption of certain other tetracyclines.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human use, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and human, has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

Indications: Vibramycin (doxycycline) has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria.

Pneumonia: Simple and multilobar pneumonia and bronchopneumonia due to susceptible strains of *Pneumococcus*, *Streptococcus*, *Staphylococcus*, *H. influenzae*, and *Klebsiella pneumoniae*.

Other Respiratory Tract Infections: Pharyngitis, tonsillitis, otitis media, bronchitis and sinusitis caused by susceptible strains of β -hemolytic *Streptococcus*, *Staphylococcus*, *Pneumococcus*, and *H. influenzae*.

Genitourinary Tract Infections: Pyelonephritis, cystitis, urethritis caused by susceptible strains of the *Klebsiella-Aerobacter* group, *E. coli*, *Enterococcus*, *Staphylococcus*, *Streptococcus*, and *Neisseria gonorrhoeae*. Gonococcal urethritis in the male has been effectively treated by Vibramycin (doxycycline) at a dose of 100 mg. i.i.d. for a single day, but highest cure rates were achieved by a dose of 50 to 100 mg. b.i.d. for two to four days. Adult females with acute gonorrheal infections may require more extended therapy.

Soft-Tissue Infections: Impetigo, furunculosis, cellulitis, abscess, infected traumatic and postoperative wounds, paronychia caused by susceptible strains of *Staphylococcus aureus* and *albus*, *Streptococcus*, *E. coli*, and the *Klebsiella-Aerobacter* group. In the treatment of soft-tissue infections, indicated surgical procedures should be carried out in conjunction with Vibramycin (doxycycline) treatment.

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include infections caused by susceptible organisms, such as:

Ophthalmic Infections: Due to susceptible strains of *Gonococci*, *Staphylococci*, and *H. influenzae*.

Gastrointestinal Infections: Due to susceptible strains of such organisms as *E. histolytica*, pathogenic *E. coli*, and species of *Shigella* and *Salmonella*.

Miscellaneous: Other infections due to susceptible strains of *Bacteroides*, *Pasteurella*, *Brucella* (in combination with streptomycin), *Psittacosis*, *Listeria*, *Rickettsia*, *Mycoplasma pneumoniae* (Eaton agent, PPO), *H. pertussis*, *B. anthracis*, *C. welchii*, *N. meningitidis*, *spirochetes* (Treponema), *Donaovium granulomatis*, and prostaticitis and trigonitis due to *Proteus* or *Pseudomonas*.

Vibramycin (doxycycline) may be useful in the treatment of acne vulgaris and acne conglobata.

Contraindications: This drug is contraindicated in individuals who have shown hypersensitivity to it.

Warnings: If renal impairment exists, even usual doses may lead to excessive systemic accumulation of the drug and possible hepatic toxicity. Under such conditions, lower than usual doses are indicated and if treatment is prolonged, Vibramycin (doxycycline) serum level determinations may be advisable.

As with other tetracyclines, Vibramycin (doxycycline) may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines.

Though not observed in clinical studies to date and until evidence to the contrary develops, it should be anticipated that, like other tetracyclines, the use of Vibramycin (doxycycline) during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of teeth (yellow-gray brownish). This tetracycline effect is more commonly associated with long-term use of the drug, but has been known to occur with treatment of short duration.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving therapeutic doses of tetracyclines. Although the mechanism of this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight during the use of this drug. This reaction may also be produced by other tetracycline derivatives and is usually of the photoallergic type. Individuals with a history of photosensitive reactions should be instructed to avoid exposure to direct sunlight while under treatment with tetracycline drugs, and treatment should be discontinued at first evidence of skin discomfort.

Precautions: The use of antibiotics may occasionally result in overgrowth of non-susceptible organisms. Constant observation of the patient is essential. If a resistant infection appears, the antibiotic should be discontinued and appropriate therapy instituted.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including dark-field examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature, may occur but are rare. Glossitis, stomatitis, proctitis, ancylostomiasis and discoloration of the nails may rarely occur during tetracycline therapy as with other antibiotics. If severe adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported; the significance of which is not known at this time.

Dosage: The usual dose of Vibramycin (doxycycline) is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg./lb. of body weight may be used. For children over 100 lbs. the usual adult dose should be used.

Therapy should be continued beyond the time that symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuation of Vibramycin (doxycycline). When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline), unlike certain other tetracyclines, is not markedly influenced by simultaneous ingestion of food or milk.

Simultaneous administration of aluminum hydroxide gel given with tetracycline antibiotics including Vibramycin (doxycycline) has been shown to decrease absorption.

Supply: Vibramycin Hyclate (doxycycline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline; bottles of 50. Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5 cc. (each teaspoonful), with a pleasant-tasting, raspberry flavor. 2 oz. bottles.

Pfizer
LABORATORIES DIVISION
New York, N.Y. 10017

VIBRAMYCIN®

MONOHYDRATE AND HYCLATE (DOXYCYCLINE MONOHYDRATE AND HYCLATE)

Description

Vibramycin (doxycycline) is a new broad-spectrum antibiotic synthetically derived from methacycline, available as Vibramycin Monohydrate (doxycycline monohydrate) and Vibramycin Hyclate (doxycycline hydrochloride hemiethanolate hemihydrate). The chemical designation of this light-yellow crystalline powder is α -6-deoxy-5-oxytetracycline. Vibramycin (doxycycline) possesses the following useful properties not observed with previously available tetracyclines: its greater absorption from the gastrointestinal tract and its capability for once-a-day maintenance dosage.

Actions

Vibramycin (doxycycline) is a broad-spectrum antibiotic and has been shown to be active *in vitro* against both gram-positive and gram-negative organisms. *In vivo* animal protection studies (PD₅₀) in mice and extensive clinical use in man have verified that Vibramycin (doxycycline) is a potent and effective antibiotic.

Vibramycin (doxycycline) differs from other tetracyclines by virtue of its greater absorption after oral administration and prolonged duration of *in vivo* antibacterial activity. Because of these factors, therapeutic effectiveness can be achieved by once-a-day maintenance dosage. Vibramycin (doxycycline) in therapeutic doses, given once daily, will produce serum activity usually persisting for 24 to 36 hours after discontinuation of therapy.

Vibramycin (doxycycline) has been administered to 60 normal volunteers for 70 days at a dose of 200 mg./day without evidence of increased toxicity.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline) is not notably influenced by the ingestion of food or milk, which do impair the absorption of certain other tetracyclines.

Animal Pharmacology

As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastro-intestinal intolerance has been seen in both dogs and monkeys.

Indications

Vibramycin (doxycycline) has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria.

Pneumonia.—Single and multilobe pneumonia and bronchopneumonia due to susceptible strains of *Pneumococcus*, *Streptococcus*, *Staphylococcus*, *H. Influenzae*, and *Klebsiella pneumoniae*.

Other Respiratory Tract Infections.—Pharyngitis, tonsillitis, otitis media, bronchitis and sinusitis caused by susceptible strains of β -hemolytic *Streptococcus*, *Staphylococcus*, *Pneumococcus*, and *H. Influenzae*.

Genitourinary Tract Infections.—Pyelonephritis, cystitis, urethritis caused by susceptible strains of the *Klebsiella-Aerobacter* group, *E. coli*, *Enterococcus*, *Staphylococcus*, *Streptococcus*, and *Neisseria gonorrhea*. Gonococcal urethritis, in the male has been effectively treated by Vibramycin (doxycycline) at a dose of 100 mg. t.i.d. for a single day, but highest cure rates were achieved by a dose of 50 to 100 mg. b.i.d. for two to four days. Adult females with acute gonorrheal infections may require more extended therapy.

Soft Tissue Infections.—Impetigo, furunculosis, cellulitis, abscess, infected traumatic and postoperative wounds, paronychia, caused by susceptible strains of *Staphylococcus aureus* and *albus*, *Streptococcus*, *E. coli*, and the *Klebsiella-Aerobacter* group. In the treatment of soft tissue infections, indicated surgical procedures should be carried out in conjunction with Vibramycin (doxycycline) treatment.

Since Vibramycin (doxycycline) is a member of the tetracycline series of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines. These include infections caused by susceptible organisms, such as:

Ophthalmic Infections.—Due to susceptible strains of Gonococci, Staphylococci, and *H. Influenzae*.

Gastrointestinal Infections.—Due to susceptible strains of such organisms as *E. histolytica*, pathogenic, *E. coli*, and species of Shigella and Salmonella.

Miscellaneous.—Other infections due to susceptible strains of *Bacteroides*, *Pasteurella*, *Brucella* (in combination with streptomycin), *Psittacosis*, *Listeria*, *Rickettsia*, *Mycoplasma pneumoniae* (Eaton agent, PPLO), *H. Pertussis*, *B. anthracis*, *C. welchii*, *N. Meningitidis*, spirochetes (*Treponema*), *Donovania granulomatosa*, and prostatitis and trigonitis due to *Proteus* or *psuedomonas*.

Vibramycin (doxycycline) may be useful in the treatment of *aene vulgaris* and *aene conglobata*.

Contraindications

This drug is contraindicated in individuals who have shown hypersensitivity to it.

Warnings

If renal impairment exist, even usual doses may lead to excessive systemic accumulation of the drug and possible hepatic toxicity. Under such conditions, lower than usual doses are indicated and if treatment is prolonged, Vibramycin (doxycycline) serum level determinations may be advisable.

As with other tetracyclines, Vibramycin (doxycycline) may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines.

Though not observed in clinical studies to date and until evidence to the contrary develops, it should be anticipated that, like other tetracyclines, the use of Vibramycin (doxycycline) during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of teeth (yellow-gray-brownish). This tetracycline effect is more commonly associated with long term use of the drug, but has been known to occur with treatment of short duration.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving therapeutic doses of tetracyclines. Although the mechanism of this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight during the use of this drug. This reaction may also be produced by other tetracycline derivatives and is usually of the photoallergic type. Individuals with a history of photosensitivity reactions should be instructed to avoid exposure to direct sunlight while under treatment with tetracycline drugs, and treatment should be discontinued at first evidence of skin discomfort.

Precautions

The use of antibiotics may occasionally result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If a resistant infection appears, the antibiotic should be discontinued and appropriate therapy instituted.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including dark-field examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions

Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature may occur but are rare. Glossitis, stomatitis, proctitis, onycholysis and discoloration of the nails may rarely occur during tetracycline therapy as with other antibiotics. If severe adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

Dosage

The usual dose of Vibramycin (doxycycline) is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended. The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg./lb. of body weight may be used. For children over 100 lbs. the usual adult dose should be used.

Therapy should be continued beyond the time that symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 or 36 hours following discontinuation of Vibramycin (doxycycline). When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Studies reported to date indicate that the absorption of Vibramycin (doxycycline) unlike certain other tetracyclines, is not markedly influenced by simultaneous ingestion of food or milk.

Simultaneous administration of aluminum hydroxide gel given with tetracycline antibiotics including Vibramycin (doxycycline) has been shown to decrease absorption.

Supply

Vibramycin Hyclate (doxycycline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline: bottles of 50. Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing, when reconstituted, doxycycline monohydrate equivalent to 25 mg. of doxycycline/5cc. (each teaspoonful), with a pleasant tasting, raspberry flavor: 2 oz. bottles.

PFIZER LABORATORIES,
Division of Chas. Pfizer & Co., Inc., New York, N.Y.

(Whereupon, at 11:25 a.m., the hearing adjourned until Thursday, September 19, 1968, at 9:30 a.m.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, SEPTEMBER 19, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:45 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. Our witness this morning is Dr. Harvey Minchow, Acting Director, Bureau of Medicine, Food and Drug Administration. We appreciate having you here this morning, Dr. Minchow. You may present your statement in any way you see fit.

Did you wish to present some response to the statement made by the company yesterday?

STATEMENT OF DR. B. HARVEY MINCHEW, ET AL.—Resumed

Dr. MINCHEW. Yes, sir; with your permission I would like to do that.

Senator NELSON. Please go ahead.

Dr. MINCHEW. After my testimony yesterday on Vibramycin, Chas. Pfizer & Co., Inc., issued a press release and statement¹ taking exception to it. My testimony was based on the records and my own knowledge of the events in which I participated. We stand on the statement. We have the following comments on the eight points made in Pfizer's press release:

(1) Pfizer said that they were shocked and disappointed at my statement that the original submission for approval of Vibramycin was "inadequate and additional data were required."

This submission was inadequate and the details of the inadequacies were discussed with the company. This is not unusual at this stage of review of any new antibiotic.

(2) Pfizer said that it did not feature labeling claims that emphasize the safety and effectiveness of Vibramycin in comparison with established products. Our statement that they did seek to feature a "broader antibiotic spectrum" refers not only to the quoted paragraph in the Pfizer statement concerning the in vitro activity, which clearly claims

¹ See statement beginning at p. 3647, *infra*.

"greater in vitro activity against a variety of Gram-positive organisms including *Staphylococcus aureus* * * *" but also the proposal of the company in their original package insert to claim efficacy for infections due to unspecified species of *Proteus* and *Pseudomonas* organisms.

(3) My statement regarding the efforts of the company to claim the advantage of not causing teeth discoloration is based on the facts. Labeling submitted but not approved, contained the following statement in conjunction with the description of the in vitro studies on calcium binding: "Less Vibramycin may be deposited in bones or teeth."

(4) My answer to the statement made by Pfizer of their reluctance to refer to thyroid darkening effects in certain animals in the package insert was adequately discussed yesterday.

(5) I have reviewed the series of meetings between January and July of 1967 and the original statement I gave is accurate. The file shows that final concurrence with all of the changes the Bureau believed necessary in the package insert was not obtained until July 31.

It is true, as Pfizer stated, that our meetings to discuss the package insert were conducted on a cordial and mutually respectful basis. We do not imply that it is somehow improper for industry to disagree with FDA on a medical matter.

(6) Pfizer has stated that at the time of their telephone call to Dr. Goddard on July 7, 1967, it was their understanding that "a decision on the generic name was all, to our knowledge, that was holding up the approval of the application." The file shows that as late as June 28, 1967, in a meeting with Pfizer they had not agreed to include the animal pharmacology section of the labeling and that other features of the final approval had not been resolved.

(7) Pfizer point No. 7 is to the effect that the Division of Anti-Infective Drugs approved their visual aid in August, and that Pfizer was justified in printing it on that approval.

Representatives of the company were told that the approval of the Division of Anti-Infective Drugs should only be tentative. They were advised of a recently established policy which required that initial advertising material would be studied elsewhere in the Bureau and formal approval would come from the Office of the Director of the Bureau of Medicine.

We will be glad to supply the committee with the memorandums of our conferences with Pfizer about this visual aid.

Taking into account all of the facts, including the fact that the four-color spread had been printed and that the detail force was en route to training sessions, Dr. Herbert L. Ley, Jr., then Director of the Bureau of Medicine, agreed to permit the use of that visual aid for a period of not more than 4 weeks from the date of the meeting on September 5, 1967. Four weeks was agreed upon because of the prolonged nature of the planned training period and the length of time required to print a new and corrected four-color visual aid. The company promised that it would expedite this.

The company asked that, if near the end of the 4-week period the new version had not been received, some of their detail men might use the old version on condition that they not direct the doctor's attention to the improper copy and not leave the detail aid with the

doctor. This last request was agreed to. Actually, that contingency is not involved here. Pfizer detail men made the misrepresentations on October 25, 1967, at the American Academy of Pediatrics meeting. This was long after the 4-week period agreed to on September 5, 1967. It was after the visual aid had been reproduced with corrections.

(8) Pfizer's contention that the statement concerning the deposition of tetracycline in bones and teeth was inserted at the request of a medical officer I cannot verify in our records. At any rate, the record is clear that this statement was strongly proffered by Pfizer and officially objected to by the Bureau of Medicine.

Senator NELSON. Thank you very much.

(The statement of Chas. Pfizer & Co. follows:)

STATEMENT BY CHAS PFIZER & CO., INC., REGARDING TESTIMONY PRESENTED BY DR. B. HARVEY MINCHEW, ACTING DIRECTOR, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION

We regret to say that Dr. Minchew's testimony is marked by serious distortions of fact, by omission of important fact, and in some cases by actual departures from the facts.

We object in the strongest possible terms to the adverse impression that Dr. Minchew's testimony creates. Our work with the FDA in seeking this approval was carried forward with thoroughness, with conscientiousness, and in a cooperative spirit. In fact, we were complimented by FDA on more than one occasion during the course of obtaining approval for Vibramycin for the thoroughness of our submission.

We are presenting herewith some examples of the grave inaccuracies and distortions contained in Dr. Minchew's testimony:

1. We were shocked and disappointed at Dr. Minchew's statement that the original submission of our application for approval of Vibramycin was "inadequate and additional data were required." This is not true. These are the facts. Representatives of the various divisions of FDA who reviewed this application were extremely complimentary about its content and organization. At no time did FDA ever tell us that more data were needed to prove the drug to be safe and efficacious. Nor did FDA ever tell us that the data we originally submitted were not an adequate basis for its approval.

Dr. Minchew's next sentence, referring to submission of additional clinical reports, carries the implication that this submission was made in order to fill a need that FDA had advised us existed. Any such implication is totally erroneous. Clinical studies on this drug, as is usual, were continued during the time of the review of the application by FDA, and periodically we submitted to FDA the results of those continuing studies. This is the type of clinical data to which Dr. Minchew refers in his statement.

2. Referring to Pfizer's original proposed package insert, Dr. Minchew commented that we tried to include features that would emphasize its safety and effectiveness in comparison with established products. As one illustration, he stated that we tried to claim "a broader antibiotic spectrum."

This is not so. Our proposed statement on the spectrum of action of Vibramycin was as follows:

"Vibramycin (doxycycline) is a broad spectrum antibiotic and has been shown to be active *in vitro* against both Gram-positive and Gram-negative organisms. It exhibits greater *in vitro* activity against a variety of Gram-positive organisms, including *Staphylococcus aureus* and less activity against some Gram-negative organisms than is seen with other tetracyclines."

This statement did not amount to a claim for a broader spectrum, but merely set forth its relative potency against Gram-negative and Gram-positive organisms. In other words, as we interpreted the scientific data, Vibramycin, as compared with certain other tetracyclines, appeared to have greater activity against a variety of Gram-positive organisms in test tubes, and less activity against some Gram-negative organisms.

3. Dr. Minchew also indicated that in our original package insert proposal we attempted to claim "an advantage in not causing tooth discoloration." This is completely untrue. The following statement in our original proposed package

insert on this subject was approved verbatim by FDA and appears in our currently approved package insert:

"Though not observed in clinical studies to date and until evidence to the contrary develops, it should be anticipated that, like other tetracyclines, the use of Vibramycin (doxycycline) during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of the teeth (yellow-gray-brownish). This tetracycline effect is more commonly associated with long term use of the drug, but has also been known to occur with treatment of short duration."

4. Dr. Minchew did not accurately state the reason for our reluctance to refer to thyroid darkening effects in certain animals in the package insert for Vibramycin. Our position simply was that such effects are observed with virtually all tetracyclines, and this had been known for several years, and yet FDA had not required any reference to this effect in earlier package inserts. We were completely willing to refer to these effects for Vibramycin if FDA required the package insert for the other tetracyclines to be revised to contain a similar reference. We felt somewhat strongly on this point since the degree of darkening observed with Vibramycin was somewhat less than with some of the other tetracyclines. Nevertheless, in the interest of moving the application along, we acquiesced.

5. Dr. Minchew's statement creates the impression that from January of 1967 through sometime in July of that year there was a whole series of meetings between Pfizer and FDA to discuss the content of our package insert, and that we were constantly unwilling to accept suggestions that the FDA representatives made. The facts are that there were only a very few meetings to discuss our proposed package insert, and at these meetings there was an honest exchange of views between our physicians and those of FDA. On some points, FDA conceded to our position and on others we conceded to theirs. We came away from at least two of these meetings with the understanding that agreement had been reached about package insert content only to learn subsequently that FDA officials had reversed themselves, or been reversed by others in FDA and additional changes were required. We felt that meetings with FDA to discuss our package insert were conducted on a cordial and mutually respectful basis. The tone of Dr. Minchew's statement belies this, and goes so far as to imply that it is somehow improper for industry to disagree with FDA on a medical matter.

6. Dr. Minchew did not accurately reflect the telephone conversation to which he referred which took place on July 7 between the representative of Pfizer and Commissioner Goddard concerning the delay in approval of this application. This telephone conversation dealt with one point only—the delay from February through the date of the call in resolving the different views among FDA personnel as to the appropriate generic name to be used for the drug. At that time, a decision on the generic name was all, to our knowledge, that was holding up approval of the application. When Dr. Goddard learned of this, he immediately made a decision as to the generic name for the drug and the final stages of approval proceeded thereafter at the expected rate.

On the subject of delay, however, it is pertinent to note that Dr. Minchew's testimony admits that on February 15, 1967 the review had been completed of the pharmacology, clinical data and chemical controls. It was not until *over six months later* that final approval of the application was granted.

7. Dr. Minchew testified at some length concerning the difficulties connected with approval of our original "visual aid" for Vibramycin, and we must take exception to the accuracy of much of his testimony on this subject.

The fact is that on August 16 we received approval from the Division of Anti-Infective Drugs of the copy for this visual aid. Based on past experience, approval by this Division, was final FDA approval for promotional materials. This approval was given by them with full understanding that it was our intention to print this material immediately. This was not a "tentative" approval of our copy, as Dr. Minchew stated, nor was he correct in stating that "it was pointed out to us that other approvals would be required."

Therefore, it came as a complete surprise to us to learn after we had printed the visual aid material on the basis of the approval received by the Division of Anti-Infective Drugs that a further review of the copy was to be made by the Bureau of Medicine.

We later learned that a change in procedure, to require such an additional review, had just been instituted by FDA without any knowledge of this change being transmitted to us.

We immediately telephoned Washington to ask for a meeting, explaining that we had in good faith printed our visual aid materials on the basis of the approval already received. And such a meeting was held.

Under these circumstances, we are at a loss to explain Dr. Minchew's reference that at this meeting we "unexpectedly" informed FDA that we had already printed the visual aid.

In view of the actual facts as stated above, we take strong exception to the statements by Dr. Minchew, which suggest that we printed the visual aid in order to create a "subtle kind of pressure to approve it, or at least to hold the required changes to an absolute minimum."

We are astonished by the further statements by Dr. Minchew that the FDA permitted us to use the visual aid that we had printed merely at the training sessions for our detail men, and that we had assured him that the revisions that FDA suggested would be made before that printed material could be used for detailing. The fact is that FDA specifically permitted us to utilize this printed material in detailing for a period of 30 days.

Dr. Ley himself acknowledged that the confusion about the earlier "approval" by the Division of Anti-Infective Drugs was largely contributed to by the Food and Drug Administration itself, and for the reason he permitted this use, though he required that certain changes be made in the detail material to be used after 30 days.

8. There is one comment which we feel compelled to make about Dr. Minchew's listing of two "major corrections" that Pfizer was required to make in the Vibramycin visual aid. One of those corrections related to the question of whether less Vibramycin will be deposited in the teeth and bones of children, than with other tetracyclines. That claim was placed in our visual aid, at the suggestion of a physician in FDA's Bureau of Anti-Infective Drugs.

Senator NELSON. You may proceed and present your statement.

Dr. MINCHEW. Mr. Chairman, I am glad to respond to your request to discuss with your committee the background of Dynapen, especially the activities of the sponsor in advertising and promoting this antibiotic to physicians.

Dynapen is the trade name given to dicloxacillin by Bristol Laboratories, Syracuse, N.Y. Dicloxacillin is the newest member of the class of semisynthetic penicillin. Many of these penicillins have the property of being resistant to destruction by penicillinase, an enzyme produced by several bacteria, including some strains of staphylococci, which inactivate the original penicillin, penicillin G, and other similar penicillins. Thus, they are clinically useful in treating staphylococcus infections that would not respond to regular penicillin therapy. There are several penicillinase-resistant penicillins on the market, each with slightly different properties: methicillin, nafcillin, oxacillin, cloxacillin, and the drug under consideration, dicloxacillin.

Senator NELSON. You say, "Many of these penicillins have the property of being resistant to destruction by penicillinase." Is penicillinase the drug that is used in those cases where there is a dramatic reaction, allergic reaction to the penicillin?

Dr. MINCHEW. There is a marketed product of penicillinase, which is used on the grounds that it neutralizes the penicillin.

Senator NELSON. In this, as I recall, one of the problems with penicillin in the beginning, and I think it still is, that some people have a dramatic reaction to it and penicillinase was developed as a neutralizer of the penicillin itself; is that correct?

Dr. MINCHEW. It was not developed for that purpose. The penicillinase itself is actually an enzyme produced by the bacteria, so that it was not a synthetically developed chemical. It is an enzyme produced by the bacteria.

Senator NELSON. But is it used for the purpose of neutralizing allergic effects?

Dr. MINCHEW. Yes, sir.

Senator NELSON. And the semisynthetic ones do not react to the penicillinase?

Dr. MINCHEW. Well, the semisynthetic ones resist destruction by penicillinase. When the penicillinase acts on the penicillin, it breaks a particular bond in the penicillin molecule called the beta-lactam ring, and in doing so renders the penicillin inactive against the bacteria.

Senator NELSON. Does that mean that if a patient has an allergic, a seriously allergic reaction to some of the semisynthetics, that there is no neutralizer then available on the market?

Dr. MINCHEW. Penicillinase would not be an effective neutralizer.

Senator NELSON. Is there any other?

Dr. MINCHEW. Not in this sense, no, sir; not in this enzymatic sense. There are other drugs for the treatment of reaction to allergy but not penicillinase.

Senator NELSON. Are they effective drugs?

Dr. MINCHEW. Yes, sir, and also they would be in an emergency situation even with regular penicillin more effective than penicillinase in neutralizing the allergic reaction.

Senator NELSON. I see.

Dr. MINCHEW. Dicloxacillin was developed in the Beecham Research Laboratories, in England, and Bristol Laboratories' application form 5 to market the antibiotic in the United States was submitted to the Food and Drug Administration on November 10, 1965. Bristol's notice of claimed investigational exemption for a new drug had been submitted April 23, 1964. (Two other U.S. firms, Ayerst and Wyeth, also submitted NDA's for dicloxacillin to the FDA at approximately the same time Bristol did.)

It has been longstanding FDA position that all penicillinase-resistant penicillins should be primarily reserved for the treatment of infections caused by penicillinase-producing staphylococci, or for the initiation of therapy when there is strong reason to believe that this type of staphylococcus is responsible. The basis for this is that routine use of the semisynthetic penicillins carries the possibility of development of resistance of staphylococci to these penicillinase-resistant penicillins and destroying their effectiveness in treating penicillin-resistant staph infections. These are the strains of staphylococci that had been responsible for the serious outbreaks of so-called "hospital staph" epidemics throughout the country in the 1950's. It was the development by Bristol, in 1960, of methicillin, the first member of this family, that largely modified this grave situation.

FDA concern on this matter has been clear since early 1963. In May of that year Dr. Charles Lewis, then Chief of the Bureau of Medicine's Division of Antibiotic Drugs, wrote to Bristol Laboratories, concerning the labeling of their semisynthetic penicillin, Prostaphlin (oxacillin):

"At some appropriate place in bold type, you should point out that the administration of Prostaphlin (sodium oxacillin) for infections which will respond to penicillin G is inadvisable because uncritical use of the drug may increase the possible development of resistant organisms."

On July 12, 1966, FDA wrote Bristol advising that, in order to bring proposed labeling for dicloxacillin into conformity with that of the other penicillinase-resistant, semisynthetic penicillins, the following sentence should appear in capitals or bold face at the beginning of the "Indications" section. "Hypen"—which was their proposed name at that time "is particularly suitable against infections due to staphylococci resistant to penicillin G (or phenethicillin)," and that, in addition, the following should appear in the same section: "If it is determined that the infection is not due to a penicillin G-resistant staphylococcus, a change to penicillin G or phenethicillin may be considered." This statement referring to changing or "switching" antibiotics I will refer to hereafter as the "switch" statement.

On July 13, 1966, Bristol replied, in part: "We still feel that * * * such a statement (the switch statement) is not justified by the facts. We will continue to accumulate data and will bring this to your attention as more experience becomes available so that we may review it again." However, the labeling accompanying this letter incorporated the FDA recommendations.

On July 29, 1966, Bristol submitted revised draft labeling incorporating three minor changes requested by an FDA telephone conversation. Bristol also changed the trade name of the drug to "Dynapen."

About that same time in 1966, Bristol was promoting its semisynthetic Tegopen (sodium cloxacillin monohydrate) with an advertising theme that is was an "everyday penicillin," and depicting its use in routine office practice. In October, we publicly criticized this ad campaign as offering the drug for conditions for which it had not been approved. Bristol representatives visited with us, contending that the drug was indeed suitable for everyday use, and they were told that before such a range of usefulness could be approved the company would have to provide the medical justification for labeling changes to permit it.

On November 25, 1966, Bristol submitted proposed revised labeling for their already marketed antibiotic, Tegopen (sodium cloxacillin monohydrate). In this, they had deleted the statement advising that therapy be switched to penicillin G in the event that bacteriological studies show the infecting organism not to be a penicillinase-producing staphylococcus. They made it clear that they intended this change also to apply to dicloxacillin. This submission was followed in January 1967 by a marketing report for a number of penicillins, a report intended to support Bristol's contentions that the incidence of resistant staphylococci had not risen despite widespread use of the semisynthetics.

In an attempt to resolve the labeling of dicloxacillin, the FDA, more than a year ago, sent a questionnaire to 11 recognized experts in the field of microbiology and antimicrobial therapy. Among the questions asked, two dealt directly with the problem of so-called "restrictive" use.

1. "Do you believe that penicillinase-resistant penicillins are now the drugs of choice for the routine treatment of all infections caused by Gram-positive cocci susceptible to their actions?" All 11 experts answered "No."

2. "Assuming you have initiated chemotherapy with a penicillinase-resistant penicillin in a severe infection and the patient is showing excellent clinical response but the cultures now show the causative or-

ganism to be a Beta-hemolytic streptococcus or pneumococcus, would you change chemotherapy to penicillin G or V?" Eight answered, "Yes." Two answered, "No." One said "Probably would not change."

The results of this survey were made available to the company, and on May 31, 1967, another conference took place, at which Bristol reiterated the desire to recommend dicloxacillin for infections due to all sensitive Gram-positive cocci. They argued, among other things, that the early fear that staphylococci would develop widespread resistance to semisynthetic penicillins had not been borne out by many years usage of methicillin, another semisynthetic. FDA did not agree, and on June 14, 1967, wrote Bristol stating that the package insert should include a statement to the effect that "if it is determined that the infection is not due to a penicillin G-resistant staphylococcus, a change to penicillin G or phenethicillin may be considered." On June 19, 1967, a conference was held with Bristol to discuss again the "switch" statement; our position and that of Bristol remained different.

Subsequently, Bristol polled 16 physicians using a different set of questions than the FDA had formulated. Bristol concluded that the written responses tended to support the Bristol position, namely, that a penicillinase-resistant penicillin should not be reserved for the treatment of infections due to penicillinase-producing staphylococci because the drug had been shown to be highly effective both bacteriologically and clinically in infections due to other infections, such as streptococci and pneumococci, and resistance to it was more a fear than an actuality. Bristol submitted a tabulated summary of the results of their poll on July 18, 1967.

Mr. GORDON. Dr. Minchew, may I interrupt at this point? What proof is there that the use of a synthetic penicillin carries the possibility of development of resistant staphylococci to these penicillins and destroying their effectiveness in destroying infections?

Dr. MINCHEW. We come to some of this later in the statement. We will certainly discuss it in as much detail as you want.

Mr. GORDON. All right.

Dr. MINCHEW. On August 31, 1967, the Bureau of Medicine asked the FDA Medical Advisory Board to consider this problem and give their recommendations. The Board was presented with the Bureau of Medicine position, and the expert opinions as expressed in answers to all the questions in the FDA and Bristol questionnaires. After lengthy discussion, the view was expressed that the approved prescribing information for these semisynthetic penicillins should presently continue to limit indications to permit observation for another year or two to see whether staphylococcal resistance to these agents does become a significant problem. With this concern in mind the Board voted to adopt the recommendation:

That the labeling for dicloxacillin contain three general statements:

1. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, V, or phenethicillin, because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

2. The principal indication is in treating infections due to penicillinase-producing staphylococci or in initiating therapy when there is the possibility of a resistant staphylococcal infection.

3. This product is also effective in treating infections due to streptococci, pneumococci, and penicillin-sensitive staphylococci.

These recommendations were implemented by the Bureau of Medicine and used as the basis for developing the final labeling for all three dicloxacillin products manufactured by Wyeth, Ayerst, and Bristol.

At a September 12 conference, a statement seemingly agreeable to both Bristol and FDA was composed, and on September 19, Bristol submitted proposed package inserts. However, under indications two additional paragraphs were added by the company which pertained to the development of resistant strains. On October 19, 1967, FDA wrote Bristol that approval of these changes in the package inserts could not be given.

Further telephone conversations took place in November, December, and January; and on February 23, 1968, a conference was held between Bristol and FDA at which Bristol again presented its position on resistant staphylococci. The company presented additional data in which it was demonstrated that among Bristol's employees, exposure to semisynthetic penicillins had not been associated with any nasal carriage of methicillin-resistant staphylococci aureus. It was pointed out that the data did not seem pertinent to the past major issues. Further, they were informed that the other two producers of dicloxacillin had now submitted labeling conforming to all FDA requests, and that these would be acted upon.

On February 26, 1968, Bristol submitted revised labeling for dicloxacillin which conformed to the wording requested by FDA. They expressed disagreement with the switch statement wording, but agreed to accept it. They submitted corrected package inserts on March 5, 1968.

On March 8, 1968, Dr. Ley, the then Director of the Bureau of Medicine, was notified that the Division of Anti-Infective Drugs recommended approval of the application of Bristol for sodium dicloxacillin, and that the labeling submitted was acceptable. (Similar approvals were recommended for the sodium dicloxacillin applications of Ayerst and Wyeth on that date.)

However, the company's activity took a new direction. About a month later, on April 9, 1968, the Surgeon General of the Public Health Service, Dr. William H. Stewart, acting for Dr. Philip Lee, Assistant Secretary of Health, Education, and Welfare, received a position paper critical of our actions from Mr. Thomas Corcoran, an attorney for Bristol.

We were asked to comment on that position paper, a copy of which is enclosed for the record—exhibit A.

Senator NELSON. It will be printed in the record.

(The document referred to follows:)

EXHIBIT A

The FDA has a theory (hereinafter called the reserve drug theory) that some antibiotics should be limited for use only in the treatment of resistant staphylococci infections even though some antibiotics are also concededly effective for the treatment of infections due to streptococci, pneumococci and non-resistant staphylococci. The FDA has implemented this theory by demanding that the labeling for these antibiotics (which are semi-synthetic penicillinase-resistant penicillins such as oxacillin, nafcillin, cloxacillin and most recently dicloxacillin which is awaiting FDA clearance) state in effect that if laboratory tests determine that the infection is caused by organisms that can be treated by the old line penicillin or penicillin G, the physician must be advised to stop using the semi-synthetic penicillinase-resistant penicillin.

Curiously enough, the FDA forbids an explanation of this cryptic advice in the labeling. It is understood, however, that it is based on the possibility that some time in the future, there might appear in the environment organisms resistant to semi-synthetic penicillins if they are widely used now. Thus, semi-synthetic penicillins should be reserved for future use by implementing the reserve drug theory through labeling.

However, other antibiotics which have been marketed in the last few years have labeling which omits the elements of the reserve drug theory even though they are indicated also for use in the treatment of infections caused by pneumococci, streptococci and both resistant and non-resistant staphylococci. Such drugs include gentamycin, cephalothin, cephaloridine, methacycline, doxycycline and lincomycin. FDA approval of the omission is peculiar in view of the fact that resistant staphylococci strains have previously appeared shortly after market introduction of similar classes of antibiotics including many of the tetracyclines. Most recently, resistant staphylococci strains have appeared after lincomycin was marketed.

By comparison, although there are rare staphylococci in nature resistant to these penicillins, no significant increase in pathogenic strains which are resistant to the semi-synthetic penicillins have appeared even though methicillin has been in use over eight (8) years and oxacillin for over six (6) years. In contrast, strains resistant to penicillin and penicillin G appeared and increased shortly after those drugs were introduced. This omission, particularly with respect to the labeling for cephalothin and cephaloridine, is indefensible since these drugs are primarily used in hospitals where the problem of resistant infections developing is the most serious.

There are a number of explanations based on experience as to the reasons for the development of strains resistant to some antibiotics and not others. One turns on the distinction between bacteriostatic antibiotics (where resistant strains have usually developed) and bactericidal antibiotics (where resistant strains have not usually developed). It should be noted that such semi-synthetic penicillins as dicloxacillin are bactericidal rather than bacteriostatic, while many of the antibiotics not subject to the reserve drug theory are bacteriostatic.

These random applications of the FDA's policy become even less defensible when it is understood that the failure to apply the theory to the labeling of non-semi-synthetic-penicillin antibiotics would have a patient allergic to penicillin defenseless against some future epidemic of resistant staphylococci infection.

The scientific underpinnings of the reserve drug theory are extremely questionable. But unquestionably, its application has been discriminatory, arbitrary and scientifically unsound. Most recently, by applying the reserve drug theory to dicloxacillin, the FDA is in effect applying the test of relative efficacy in reverse despite the abundant legislative history that this factor cannot be considered by the FDA in approving new drugs. The FDA has refused to approve labeling allowing the marketing of dicloxacillin for streptococci, pneumococci and sensitive staphylococci because it has been shown to be better than penicillin G and penicillin V in the treatment of bacterial infections in that it is effective against penicillin G-resistant staphylococci.

It is urged, therefore, that the FDA either immediately discard the theory by deleting its elements from the labeling for semi-synthetic penicillinase-resistant penicillins or apply it even-handedly by requiring it in the labeling for all antibiotics which are indicated for use in the treatment of infections caused by pneumococci, streptococci and staphylococci. After that, we hope the FDA should appoint a joint industry-government-academic advisory panel to decide whether the reserve drug theory itself should be finally and uniformly imposed or discarded.

MARCH 28, 1968.

Dr. MINCHEW. Our comments on this position paper are as follows, and I will be quoting for a few moments and will notify you at the end of the quote:

It is true, as Mr. Corcoran affirms, that the labeling advises the physician to use, or to change to, penicillin G when sensitivity studies indicate the pathogen is susceptible to it. It is not true, as Mr. Corcoran states, that "Curiously enough, the FDA forbids an explanation of this cryptic advice in the labeling."

The FDA did disagree with the desire of Bristol Laboratories, unique to it amongst the three companies involved, to insert into their package labeling a very extensive and discursive addition to the Medical Advisory Board's

opinion. It was believed that their proposed additional paragraphs would weaken the labeling's public-spirited appeal to physicians to reserve the use of these drugs to the serious need for which they are so uniquely valuable. For that reason, the Bureau of Medicine did not accept the Bristol addition.

Data from the National Drug Trade Index (1966) indicates that, in spite of the relatively restrictive labeling of the semisynthetic penicillins, these drugs were being widely prescribed for respiratory diseases, etc. Furthermore, the position of the Bureau has been based on the belief that liberalizing, instead of further restricting, the indications, would be followed by even more open promotion and use of these drugs as routine agents in general office practice for the treatment of common upper and lower respiratory tract infections. This would lead to a much more widespread use than has been the case in the past and could, therefore, contribute to the probability of a more rapid development of strains of staphylococci resistant to these agents. More recently, the Bureau of Medicine has become aware of reports from Switzerland, France, and Denmark of the development of increasing numbers of methicillin-resistant strains of staphylococci. (Methicillin is another semisynthetic penicillin.)

Because of these facts and concerns, and because of the permissiveness of the labeling for several of these (semisynthetic penicillin) products, e.g., oxacillin and cloxacillin, it is the intent of the Bureau of Medicine to bring the labeling for all the semisynthetic penicillins, and other antibiotics where appropriate, into consistency with its Medical Advisory Board's recommendations, and the approved dicloxacillin labeling.

Senator NELSON. May I interrupt just a moment? If the FDA considers it important that these semisynthetics not be used in circumstances where another penicillin G or another drug is effective for the purpose of avoiding development of penicillin-resistant strains to this drug, why not make much tougher labeling than you have? Obviously, it would appear from your statement that it isn't working, it isn't persuading doctors to avoid voluntarily using it when penicillin G or other penicillin will do the job, and it is in the public interest. Why shouldn't the labeling be a whole lot tougher, and simply tell the doctor, positively, "You should not use it under these circumstances"?

Dr. MINCHEW. The extent of the restrictions which had been in the semisynthetic penicillins prior to dicloxacillin was principally just a switch statement advising the physician that he should consider switching if the organism is in fact sensitive to the other penicillins. We feel that the dicloxacillin labeling we have implemented is much tighter, and is a basic labeling which would enable us to much more rigidly restrict the promotion or more widespread promotion of the drug. We do feel the dicloxacillin represents a significant tightening.

Senator NELSON. A significant what?

Dr. MINCHEW. Tightening.

Senator NELSON. But I take it you consider it important that they not be widely used to avoid the development of a resistant strain of any kind.

Dr. MINCHEW. Yes, sir.

Senator NELSON. And that this has been, and still is, a serious problem in the hospitals around the country. If that is the case, why not much more strictly limit its use with much stronger language?

Dr. MINCHEW. Our feeling is that the dicloxacillin labeling in essence restricts it to its appropriate place and that with the dicloxacillin labeling we have placed the drug in its proper place for use, and that the labeling is strict enough to enable us to limit promotion and act if promotion is outside of these very restricted indications.

Senator NELSON. What do you do in the event that the doctors

don't pay much attention to this and do the same thing that they did with chloramphenicol?

Dr. MINCHEW. Of course, what the doctor does is something that we don't have any direct authority over.

Senator NELSON. No, but you do have control over the labeling. You had control over labeling, but the advertising and promotion of chloramphenicol didn't work.

Dr. MINCHEW. Our feeling is that if the physician uses these products in keeping with the labeling of dicloxacillin he will be using it appropriately. If he is not using it in keeping with the labeling, he perhaps would not observe tighter label restrictions.

Senator NELSON. But you did decide, after the chloramphenicol hearings and the publicity on them, that you had to do something much more dramatic; so you wrote your "Dear Doctor" letters. As I understand it you wrote to the medical journals of the country and advised them, and to hospitals, and so forth, that, if this is important, then why not toughen up the labeling and put a special box in there? Just tell the doctors that one of the problems around the country has been the development of resistant strains, and so forth, of various kinds. It has created a tremendous problem, of which you are aware. These semisynthetics should be limited solely to this purpose or we are going to have exactly the same problem again, and box it in, in double black lines, and send them all a letter.

Dr. MINCHEW. We feel that the dicloxacillin labeling is tight enough in regard to being certain that the physicians have been notified of this. I think further testimony, which I will give, will show you what action has been taken in regard to seeing that all physicians have gotten a letter.

Senator NELSON. Then when it is all over with, if it ends up that the doctors haven't noticed or haven't paid any attention or the companies have continued somehow or other to blur the point by their promotional activities, and find, as we did in chloramphenicol, that it is being widely used in circumstances where it is not desirable to use it, because there is another drug that is as effective, what do you intend to do then?

Dr. MINCHEW. That, of course, we would have to respond to at the time. In this instance, as you will subsequently see, we have already responded in our relationship with the manufacturer when he promoted it outside of the labeling.

Senator NELSON. The test will be, you recite—I don't know what they did in Switzerland, France, and Denmark, but your sentence is that "More recently the Bureau of Medicine has become aware of reports from Switzerland, France, and Denmark of the development of increasing numbers of methicillin-resistant strains of staphylococci."

Supposing that develops in this country?

Dr. MINCHEW. I would like for Dr. McCleery to offer a comment here.

Dr. McCLEERY. Mr. Chairman, in some, I believe real, sense what you are asking today, what you are describing, is a process which is already underway in the aftermath of the introduction of Dynapen by promotional labeling and journal advertising which we get to later.

We found that it might indeed be desirable for the labeling for these three dicloxacillin products, as they entered the market, to be tighter

in one sense (not changed in the nature of the agreement that we reached with the companies before they went on the market). We came to feel that it might well need an "Important Note," of the kind that you are suggesting, to offer more detailed information as to what experience had occurred around the world, and why it was very important for physicians to consider the recommendations in the indications section.

So, in effect, I think we are delving, as nearly as we can see, with the problem that you are suggesting. What the response will be to this tighter and more informative labeling when it is applied to the whole class of products, of which dicloxacillin is a member, would be something that would have to be observed in somewhat the way as the Chloromycetin problem was handled.

We all believe, after considering the views of the experts that we consulted and that the company consulted, and of our medical advisory board, that this labeling is consistent with good medicine, and as much help to physicians as we felt we could—

Senator NELSON. Have you sent communications with good documentary evidence and so forth to all the medical journals in the country asking them to editorialize on this matter?

Dr. McCLEERY. No, sir.

Senator NELSON. Don't you think, if it is an important matter of public health and the practice of medicine, that you ought to use all the outlets available?

Dr. McCLEERY. Yes, sir. There already have been editorials in this country. Those editorials have appeared in such journals as the New England Journal of Medicine in 1967. These opinions of experts, both in editorials and in articles, formed a part of the basis for the stand that we took in reference to the company's request. They are available. Those opinions have been given broadly to the medical profession, and I am sure, if the need arises, that we would further consider the suggestions you make.

Senator NELSON. You have the medical schools and a whole series of outlets. It just seems to me that this is an important matter of public health, that the FDA ought to be moving heaven and earth to be sure that the education is gotten out to the profession and to be sure that the labeling is really strong enough and tough enough, so that it makes the point clear.

I understand why the companies don't like it. They won't sell as much. But the public health certainly has to come first, and there will be a continuous push by the companies to expand the use of their products. So in my judgment they will end up winning that battle, just as they did with chloramphenicol. That one went over a period of 15 or 16 years, from 1952 until right up through now, and they won the battle hands down.

Dr. McCLEERY. Well, it is certainly a logical possibility that it may occur again. We fervently hope it won't.

I might also say that one of the exhibits you will see is the remedial letter that went to 280,000-some physicians on the Dynapen problem. There was also a corrective journal ad, which we come to later, both of which were strong messages sent out by the company, in conjunction with us, that make all these points at this time. It may not be effective but we hope that it will. We will have to try to follow and see.

Senator NELSON. Well, I would understand why the companies would resist it, but it would seem to me that if it is important, there ought to be a special box in the package labeling and any place else where they advertise, and on the labeling. It seems to me you ought to single out this particular reason.

I can understand the doctor reading rapidly, the drug is good for all kinds of things, and there is a little cautionary statement to substitute other drugs when they are effective, but I don't expect it will be followed. It would seem to me you could make much tougher labeling both as to the package insert and as to the advertising in the journals, if you are going to make it work.

Now there is a big hullabaloo by the industry that the FDA is sticking its nose in our business, but, you know, they would be happy with no regulations at all. They would be happy to sell 10 times as much chloramphenicol or any of the rest of the stuff. That is their business, although I have been a little worried about their public conscience, but I am not going to trust my health and the health of the Nation to their public conscience when we have so many instances where they didn't have much of a conscience.

I think the FDA has just got to be tougher on this stuff.

Dr. McCLEERY. May I just say one more word, Senator Nelson. We share your concern, although we may not always supply the response that you might wish us to. In this instance, the class revision of labeling is already underway, in order, hopefully, to do just what you are asking; that is, the inclusion of an "Important Note" to enlarge the understanding of the physician that uses the product, so that he will be informed in the ways which I think you are suggesting would be valuable.

Senator NELSON. I hope you are successful.

Dr. McCLEERY. Thank you.

Senator NELSON. Please go ahead.

Dr. MINCHEW (reading): "On March 27, 1968, the Director of the Bureau of Medicine telephoned the vice president and medical director (Dr. Peltier) of Bristol Laboratories to explain again the basis for FDA's so-called 'restrictive' labeling for dicloxacillin. Dr. Peltier alleged that the labeling was discriminatory against this particular product.

"Dr. Ley informed him that this was so only because it was the first reflection of a new policy, and promised him that the labeling of other semisynthetic penicillins, as well as that of other appropriate antimicrobial agents, was already under study for comparable revision.

"Dr. Ley ended his telephone memo with this note, '* * * it appeared that Dr. Peltier recognized that from the Commissioner down to the working level the agency was taking the approach of restricting usage by appropriate labeling for the semisynthetic penicillins.' It is, therefore, worthy of serious note that on March 28, 1968, Bristol turned from the scientific to the legal-administrative approach, developed the copy of the argument of that date, retained attorney Thomas Corcoran to present this to the Office of the Secretary of April 9, 1968.

"Bristol, near the end of its March 28, 1968 position paper, suggests that the FDA apply the so-called 'reserve drug theory' evenhandedly or immediately discard it—this in spite of the assurance, on the day prior, of the Bureau Director that this was underway. Even more

improperly, they end their paper with this misleading suggestion: 'After that, we hope the FDA should appoint a joint industry-government-academic advisory panel to decide whether the reserve drug theory itself should be finally and uniformly imposed or discarded.'

"It is misleading because it implies that the FDA reached its position in the absence of relying, in practical fact, on such an 'advisory panel,' which was known to Bristol not to be the case. It is misleading, also, because it was known to Bristol that the FDA, as part of its decision-making process in reaching the current position, already planned to reconvene the question after an appropriate interval allowed the collection of further evidence as to the potential danger represented by labeling these agents so that they might become in legal fact 'Everyday penicillins.'"

Mr. Chairman, I thought that the background I have just related would assist you and your committee in evaluating what is to follow.

On May 7, 1968, Dr. Ley issued a letter to Bristol Laboratories advising the firm that the FDA had concluded that the drug was safe and effective for use as recommended in the labeling. A copy of the approved labeling of Dynapen is included for the record—exhibit B.

Senator NELSON. It will be printed in the record.

(The document referred to follows:)

EXHIBIT B—BRISTOL

DYNAPEN®—SODIUM DICLOXACILLIN MONOHYDRATE, CAPSULES—125 mg. and 250 mg.

DESCRIPTION

Dynapen (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazolyl penicillin series. It is the monohydrate sodium salt of 3-(2, 6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.

PHARMACOLOGY

Dynapen (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies¹ with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500, and 1000 mg.^{1,2,8} as measured at the two-hour level.

ACTIONS—(MICROBIOLOGY)

Dynapen (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci.

The average Minimal Inhibitory Concentrations (M.I.C.'s of Dynapen (sodium dicloxacillin monohydrate) for these organisms are as follows:

Average M.I.C.
(mcg./ml.)

Group A beta-hemolytic streptococcus.....	0.15
Diplococcus pneumoniae.....	0.10
Staphylococcus (nonpenicillinase-producing).....	0.20
Staphylococcus (penicillinase-producing).....	0.30

INDICATIONS

The principal indications for Dynapen (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrated the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

CONTRAINDICATION

A history of allergic reactions to penicillins should be considered a contraindication.

PRECAUTIONS

As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteroids, antihistamines).

As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should superinfection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems, is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Safety for use in pregnancy has not been established.

ADVERSE REACTIONS

Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving Dynapen (sodium dicloxacillin monohydrate). Pruritus, uricaria, skin rashes, and allergic symptoms have been occasionally encountered, as with all penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

DOSAGE

For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs.) or more: 125 mg. q.6h.

Children weighing less than 40 Kg. (88 lbs.): 12.5 mg./Kg./day in divided doses q.6h.

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg. (88 lbs.) or more: 250 mg. q.6h or higher. Children weighing less than 40 Kg. (88 lbs.): 25 mg./Kg./day or higher in divided doses q.6h.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

N.B.: Infections caused by group A Beta-Hemolytic Streptococci should be treated for at least 10 days to help prevent the occurrence of acute Rheumatic fever or acute Glomerulonephritis.

SUPPLY

Dynapen (sodium dicloxacillin monohydrate) Capsules:

List 78923—125 mg./capsule, bottles of 24.

List 78925—125 mg./capsule, bottles of 100.

List 78933—250 mg./capsule, bottles of 24.

List 78935—250 mg./capsule, bottles of 100.

Also available:

List 78566—Dynapen sodium dicloxacillin monohydrate). For Oral Suspension, 62.5 mg./5 ml., 80-ml. bottle.

REFERENCES

1. Data on file at Bristol Laboratories.

2. Bennett, J. V. Gravenkemper, C. F. Brodie, J. L., and Kirby, W. M. M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparisons with Oxacillin and Cloxacillin." *Antimicrobial Agents and Chemotherapy*, 1964, pp. 257-262.

3. Naumann, P. and Kempf, E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin." *Arzneimittel-Forschung*, 15, pp. 139-145, 1965.

BRISTOL

DYNAPEN®—SODIUM DICOXACILLIN MONOHYDRATE, POWDER FOR ORAL SUSPENSION

DESCRIPTION

Dynapen (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazolyl Penicillin series. It is the monohydrate sodium salt of 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccil infections.

PHARMACOLOGY

Dynapen (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies¹ with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxy-methyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500, and 1000 mg.^{1 2 3} as measured at the two-hour level.

ACTIONS—(MICROBIOLOGY)

Dynapen (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci.

NOTE.—Numbered footnotes at end of article, p. 3663.

The average Minimal Inhibitory Concentration (M.I.C.'s) of Dynapen (sodium dicloxacillin monohydrate) for these organisms are as follows:

Average M.I.C.
(mcg./ml.)

Group A beto-hemolytic streptococcus-----	0.05
Diplococcus pneumoniae-----	0.10
Staphylococcus (nonpenicillinase-producing)-----	0.20
Staphylococcus (penicillinase-producing)-----	0.30

INDICATIONS

The principal indications for Dynapen (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

CONTRAINDICATIONS

A history of allergic reactions to penicillins should be considered a contraindication.

PRECAUTIONS

As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteroids, antihistamines).

As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should superinfection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems, is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Safety for use in pregnancy has not been established.

ADVERSE REACTIONS

Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving Dynapen (sodium dicloxacillin monohydrate). Pruritus, urticaria, skin rashes, and allergic symptoms have been occasionally encountered, as with penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

DOSAGE

For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs.) or more: 125 mg. q.6h.

Children weighing less than 40 Kg. (88 lbs.): 12.5 mg./Kg./day in equally-divided doses q.6h.

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg. (88 lbs.) or more: 250 mg. q.6h. or higher.

Children weighing less than 40 Kg. (88 lbs.): 25 mg./Kg./day or higher in equally-divided doses q.6h.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

N.B.: Infections caused by group A beta-hemolytic streptococci should be treated for at least 10 days to help prevent the occurrence of acute rheumatic fever or acute glomerulonephritis.

DIRECTIONS FOR DISPENSING

Prepare suspension at the time of dispensing. Add a total of 45 ml. water to the bottle. For ease in preparation, first shake the bottle to loosen powder and then add the water in two portions—shake well after each addition. This will provide 80 ml. of suspension. Each 5 ml. teaspoonful will contain Dynapen (sodium dicloxacillin monohydrate) equivalent to 62.5 mg. of dicloxacillin. The reconstituted suspension is stable for 14 days under refrigeration.

SUPPLY

List 78566—Dynapen (sodium dicloxacillin monohydrate) For Oral Suspension, 62.5 mg./5 ml., 80-ml. bottle.

Also Available:

DYNAPEN (sodium dicloxacillin monohydrate) Capsules

List 78923—125 mg./capsule, bottles of 24.

List 78925—125 mg./capsule, bottles of 100.

List 78933—250 mg./capsule, bottles of 24.

List 78935—250 mg./capsule, bottles of 100.

REFERENCES

1. Data on file at Bristol Laboratories.

2. Bennett, J. V., Gravenkemper, C. F., Brodie, J. L., and Kirby, W. M. M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparisons with Oxacillin and Gloxacillin." *Antimicrobial Agents and Chemotherapy*, 1964, pp. 257-262.

3. Naumann, P. and Kempf, E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin." *Arzneimittel-Forschung*, 15, pp. 139-145, 1965.

Dr. MINCHEW. Ten days later, on May 17, 1968, an airmail letter, signed by Bristol's vice president and medical director, was sent to practicing physicians throughout the United States. This letter announced that Dynapen would be available within a week and that it "is a new specific useful in a broad range of skin and soft tissue infections." The airmail envelope also emphasized "A New High Potency Penicillin Specific for Skin and Soft Tissue Infections." Copies of the letter and envelope are included for the record—exhibits C and D.

Senator NELSON. They will be printed in the record.

(The information referred to follows:)

EXHIBIT C

BRISTOL LABORATORIES,
Syracuse, N.Y.

Re New high potency penicillin, specific for skin and soft tissue infections.

DEAR DOCTOR: Within the next week, a new high potency penicillin—sodium dicloxacillin monohydrate—will be available for use in your practice. Dynapen® (as the product is called) is a new specific useful in a broad range of skin and soft tissue infections. Its outstanding bactericidal action, its excellent oral absorption (superior to all other penicillins), and its low incidence of side effects offer a persuasive rationale for prescribing Dynapen in infections of the skin and underlying tissue where resistant staph are so often known or suspected. For example, furunculosis, carbuncles, impetigo, cellulitis, pyoderma, abscess, pustular acne, ecthyma, infected skin ulcer, lymphangitis and lymphadenitis; in postoperative infections; and in infected wounds, burns and lacerations—caused by these organisms—all are exceptionally responsive to treatment with Dynapen.

A number of facts account for the superiority of Dynapen. First of all, Dynapen is bactericidal—killing sensitive pathogens outright, rather than merely inhibiting their growth. Resistance has not developed during therapy. Yet, as you know, therapy with bacteriostatic agents such as the tetracyclines and erythromycins is frequently complicated by the development of resistance.

Not only is Dynapen bactericidal but it is so well absorbed an oral dose of 125 mg. provides averages blood levels far in excess of the concentrations necessary to kill susceptible organisms *in vitro*. The exceptionally high blood levels attained with Dynapen on oral administration make this new agent *superior in absorption to all other penicillins*. Oral doses of 125 mg. yield peak blood levels 5 times higher than 250 mg. (400,000 units) of penicillin G 2 to 4 times higher than 250 mg. of potassium penicillin V. In fact, this penicillin is so well absorbed that blood levels achieved are equal whether the drug is administered orally or intramuscularly.

During more than four years of clinical trials, Dynapen has been evaluated in thousands of patients. For example, it was prescribed at various dosage levels in the treatment of 589 patients with a variety of pathogenic staphylococcal infections. In 204 cases of sensitive staph infections, 99% were cured or improved. In 385 cases of penicillin G-resistant staph infections, 96% were cured or improved. Results obtained at the recommended dose of 125 mg. q. 6 h. in adults and 12.5 mg./kg./day in children were excellent; doubling this dose did not increase clinical effectiveness in such infections.

On the basis of reports to date, side effects with Dynapen (sodium dicloxacillin monohydrate) are exceptionally rare—approximately 1% in patients receiving the recommended dose for mild to moderate infections. The evidence to date clearly supports the contention that the lower dosage does mean a lower incidence of side effects. Of course, as with any penicillin, the possibility of allergic reactions must always be considered.

With all of these advantages, Dynapen is also comparable in cost to other antibiotics, and incidentally, it costs significantly less than most of the "cyclines" and "mycins."

In sum: bactericidal action, the highest blood levels of any oral penicillin, no direct toxicity, an excellent clinical record, a notable lack of side effects, and patient economy, are truly decisive reasons for considering Dynapen whenever you treat resistant staphylococci skin, soft tissue, postoperative and wound infections.

Please see enclosed Official Package Circulars which provide the necessary prescribing information. However, to get a real feel for the drug, may we suggest you return the Business Reply Card for clinical trial supply.

Sincerely yours,

H. C. PELTIER, M. D.,
Vice President, Medical Director.

EXHIBIT D

BRISTOL LABORATORIES
Div. of Bristol Myers Co.
Syracuse, New York 13201



VIA AIR MAIL

A *NEW*

High Potency Penicillin

Specific For

Skin and Soft Tissue Infections

Dr. MINCHEW. When we received a copy of the Dynapen promotional letter, on May 20, 1968, it was seen immediately that the letter was naming the drug for uses beyond the intent of the labeling. I asked that our Division of Medical Advertising evaluate the letter and other features of Bristol's initial advertising campaign in medical journals on the basis of the approved labeling. About the same time, an Arlington, Va., physician was given a detail piece which will be discussed.

We regarded the promotional letter announcing Dynapen as seriously misleading in a number of respects. For example:

1. The too-general main theme, "* * * penicillin for Skin and Soft Tissue Infections," invited uncritical use of Dynapen as an "everyday" penicillin when, in fact, the approved labeling restricts use of this drug to treating infections that are due to penicillin G-resistant staph.

2. The letter stated that Dynapen is a "specific useful in a broad range of skin and soft tissue infections." The implication given by "broad range" in the promotional letter was that Dynapen is indicated for infections caused by a wide variety of bacterial organisms. This is inconsistent with the limitations of use in the approved labeling.

Senator NELSON. Does Dynapen have the effectiveness on various bacteria that no other drug does? Is there any such case?

Dr. MINCHEW. Only in the area of penicillin G resistant staphylococci is it particularly valuable, but even here there are other drugs which may well work against the penicillinase producing staph. There are no bacteria for which no other drugs are effective and these are.

Senator NELSON. Is it more effective, these other drugs, than any other drugs available on the market?

Dr. MINCHEW. For the penicillinase producing staph or the others?

Senator NELSON. For the others, not the penicillinase?

Dr. MINCHEW. No, sir.

Senator NELSON. So that to implement the position of FDA on this, it ought to be solely limited to the use of penicillinase-resistant staph?

Dr. MINCHEW. Our position is that it should be limited to the treatment of penicillin-resistant staph infections or in initiating therapy when such an infection is suspected. You don't often know the resistance pattern of the staphylococcus when you first start therapy.

Senator NELSON. And if it turns out that it is not a penicillinase-resistance staph infection, it is your position that they ought to switch to penicillin G or some other, is that correct?

Dr. MINCHEW. Yes.

Senator NELSON. Do you think in your labeling, in your approved promotional ads, that this is made sufficiently clear?

Dr. MINCHEW. We believe so.

Senator NELSON. Please go ahead.

Dr. MINCHEW. 3. The promotional letter was silent both as to the need for culture and sensitivity testing, and to the need to switch therapy if a penicillin G-sensitive organism is later found to be the causative agent. We regarded these omissions as particularly misleading because it acted to encourage unapproved use of Dynapen as an "everyday" penicillin.

Mr. Chairman, the initial Dynapen letter sent to physicians was not a long letter but, in our opinion, it was misleading almost in its entirety.

The initial ad campaign in Medical World News—exhibit E—and the Medical Tribune carried the same misleading promotional impact as the promotional letter in several respects.

(The exhibit follows:)

EXHIBIT E

a new
high
potency
penicillin

outstanding bactericidal performance
in skin and soft tissue infections:*

including staphylococcal infections,
infected wounds and abscesses

Unsurpassed bactericidal activity.

Cured-improved record over 95 %.

1 % side effects at recommended dose.

Superior in absorption to all other penicillins.

No resistance has developed.

No risk of tooth-staining.

No direct toxicity reported to date. (Penicillin allergy can occur.)

Low cost therapy.

*The principal indications for Dynapen are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment in those infections where a penicillinase-producing staphylococci is suspected.

NEW

⊗ *new and specific
for skin and
soft tissue infections*

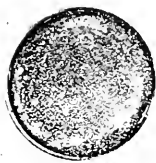
SODIUM DICLOXACILLIN MONOHYDRATE

BRISTOL

for all the facts about this new high potency penicillin >

a new high potency penicillin

outstanding bactericidal performance in skin and soft tissue infections.*
cellulitis, pyodermas, boils, abscesses, infected wounds and lacerations



control (no antibiotic)



lincomycin 1.56 mcg/ml.



tetracycline 0.20 mcg/ml.



Dynapen 0.20 mcg/ml.

Comparison of Bactericidal Dynapen with Lincomycin and Tetracycline

Blood agar plates containing minimum inhibiting concentrations of three antibiotics were inoculated with staphylococci. A fourth control dish without antibiotic was also inoculated. All were incubated overnight (top row). All three antibiotics prevented growth. Then, three new blood agar plates (without antibiotic) were inoculated with material from each antibiotic plate and again incubated overnight. Staphylococci were cultured from the material taken from the plates that had contained lincomycin and tetracycline. No staphylococci were grown from the Dynapen plate.



subculture from lincomycin plate



subculture from tetracycline plate



no growth from Dynapen plate

Unsurpassed bactericidal activity.

Dynapen kills sensitive pathogens outright rather than merely inhibiting growth.

Tooth-staining does not occur.

The fact that Dynapen can be used without risk of tooth-staining is an important consideration in the treatment of children.

Resistance does not develop.

Resistance to Dynapen does not develop during therapy as is frequently the case with bacteriostatic agents.

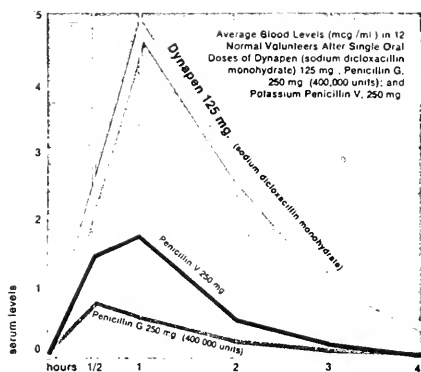
No direct toxicity has been reported to date.

No blood dyscrasias, hepatotoxicity or photosensitivity have been reported with Dynapen. Of course, as with any penicillin, the possibility of allergic reactions must be considered.

NEW
Dynapen®
SODIUM DICLOXACILLIN MONOHYDRATE

new and specific
for skin and
soft tissue infections

BRISTOL



Unexcelled absorption.

In oral doses of 125 mg., Dynapen (sodium dicloxacillin monohydrate) yields peak blood levels 5 times higher than 250 mg. (400,000 units) of penicillin G, 2 to 4 times higher than 250 mg. of potassium penicillin V. In fact, this new high potency penicillin is so well absorbed that blood levels achieved are equal whether the drug is administered orally or intramuscularly.

Low cost therapy.

With all of its advantages, Dynapen is comparable in cost to other leading brands of penicillin, and costs significantly less than brand-name broad or medium spectrum "cyclines" and "mycins."

*The principal indications for Dynapen are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment in those infections where a penicillinase-producing staphylococci is suspected.

THE CLINICAL RECORD

Outstanding cured-improved record. Excellent results were obtained at the doses recommended for mild-to-moderate infections (125 mg. q. 6h. for adults; 12.5 mg./Kg./day for children under 40 Kg.).

Dynapen In Coagulase Positive Staphylococcal Infections

125 mg. Capsules	131 Patient
Clinical Response	
Cured	99
Improved	30
Unimproved or Worse	2
Bacteriological Response	
Normal Flora/No Growth	113
Superinfection	1
Resistance	5
Carrier or Residual Infection	12

250 mg. Capsules	268 Patient
Clinical Response	
Cured	224
Improved	61
Unimproved or Worse	3
Bacteriological Response	
Normal Flora/No Growth	265
Superinfection	2
Resistance	3
Carrier or Residual Infection	16

62.5 mg./5 ml. or 125 mg./5 ml. Suspension	227 Patient
Clinical Response	
Cured	194
Improved	31
Unimproved or Worse	2
Bacteriological Response	
Normal Flora/No Growth	214
Superinfection	3
Resistance	—
Carrier or Residual Infection	10

1% side effects in recommended doses for mild to moderate infections. On the basis of all reports to date, side effect (limited primarily to mild GI upsets) are exceptionally rare—less than 1% in patients receiving the 125 mg. and the 62.5 mg./5 ml. formulations.

Adverse Reactions to Dynapen

Formulations	Dosage Schedule	Number of Patients	Number of Side Effect
Total		1510*	35* (2.3%)
125 mg. capsules	q. 6h.	379	5 (1.3%)
62.5 mg./5 ml. oral suspension	q. 6h.	133	0 (0%)
250 mg. capsules	q. 6h.	479	21 (4.4%)
125 mg./5 ml. oral suspension	q. 6h.	422	7 (1.6%)

*Side effects occurred in 2 of 97 patients treated at other dosages.

These data clearly support the contention that the low dosage means a lower incidence of side effects.

for prescribing information see next two pages

a new high potency penicillin

outstanding bactericidal
performance in skin
and soft tissue infections:
cellulitis, pyodermites, boils,
abscesses, infected
wounds and lacerations



TEXT OF OFFICIAL PACKAGE CIRCULAR-DI-7891-2-1 March, 1968

Description: DYNAPEN (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazolyl penicillin series. It is the monohydrate sodium salt of 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.

Pharmacology: DYNAPEN (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies¹ with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500, and 1000 mg.^{1,2,3} as measured at the two-hour level.

Actions (Microbiology): DYNAPEN (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci.

The average Minimal Inhibitory Concentrations (M.I.C.'s) of DYNAPEN (sodium dicloxacillin monohydrate) for these organisms are as follows:

	Average M.I.C. (mcg./ml.)
Group A beta-hemolytic streptococcus	0.05
Diplococcus pneumoniae	0.10
Staphylococcus (nonpenicillinase-producing)	0.20
Staphylococcus (penicillinase-producing)	0.30

Indications: The principal indications for DYNAPEN (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

Contraindications: A history of allergic reactions to penicillins should be considered a contraindication.

Precautions: As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteroids, antihistamines).

Guide to principal indications

Skin and soft tissue infections such as:

Furunculosis	Abscess
Carbuncles	Pustular acne
Impetigo	Infected skin ulcer
Ecthyma	Lymphangitis
Cellulitis	Lymphadenitis
Pyoderma	

as well as infected wounds, burns and lacerations



125 mg capsules



highly palatable Oral Suspension, 62.5 mg./5 ml., that eliminates the penicillin taste.

Dosage guide

Usual adult dose for mild to moderate infections: 125 mg. q. 6h.*

Usual children's dose for mild to moderate infections: 12.5 mg./Kg./day in four equally divided doses*

*Higher and/or more frequent doses should be used for more severe infections.

NEW

® new and specific for skin and soft tissue infections

SODIUM DICLOXACILLIN MONOHYDRATE

As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should superinfection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems, is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Safety for use in pregnancy has not been established.

Adverse Reactions: Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving DYNAPEN (sodium dicloxacillin monohydrate). Pruritus, urticaria, skin rashes, and allergic symptoms have been occasionally encountered, as with all penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

Dosage: For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs.) or more: 125 mg q. 6h.

Children weighing less than 40 Kg. (88 lbs.): 12.5 mg./Kg./day in divided doses q. 6h.

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg. (88 lbs.) or more: 250 mg q. 6h or higher.

Children weighing less than 40 Kg. (88 lbs.): 25 mg./Kg./day, or higher, in divided doses q. 6h.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

N.B.: Infections caused by Group A beta-hemolytic streptococci should be treated for at least 10 days to help prevent the occurrence of acute rheumatic fever or acute glomerulonephritis.

Supply:

List 78923—DYNAPEN (sodium dicloxacillin monohydrate) Capsules, 125 mg., bottles of 24.

Also available:

List 78566—Oral Suspension, 62.5 mg./5 ml., 80 ml. bottle.

References: 1. Data on file at Bristol Laboratories. 2. Bennett, J. V., Gravenkemper, C. F., Brodie, J. L., and Kirby, W. M. M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparisons with Oxacillin and Cloxacillin," Antimicrobial Agents and Chemotherapy, 1964, pp. 257-262. 3. Naumann, P. and Kempf, E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin," Arzneimittelforschung, 15, pp. 139-145, 1965.



Bristol Laboratories
Division of Bristol-Myers Co.
Syracuse, New York 13201

Dr. MINCHEW. On Friday, May 24, 1968, the then Commissioner Goddard telephoned Mr. Morris Weeden, president of Bristol Laboratories, informed him that the certificates for marketing the drug had been withdrawn, and offered to meet with him at 9 a.m., Monday, May 27, to discuss Bristol's Dynapen promotional campaign.

Senator NELSON. What do you mean, certificates for marketing the drug? Are you saying you wouldn't do it?

Dr. MINCHEW. All antibiotics go through the certification procedure, and when they meet the standards of identity, strength, quality, and purity, there is issued a certificate which legally allows them to enter interstate commerce. Commissioner Goddard withdrew those certificates.

Senator NELSON. Which meant you withdrew the drug from the market?

Dr. MINCHEW. Which meant that the drug in interstate commerce was then illegal.

Senator NELSON. And was that amount of the drug which was already in the marketplace withdrawn?

Dr. MINCHEW. We will come to that subsequently. During that weekend, action was taken to determine the extent of the distribution of Dynapen, including all lots initially certified. All shipments were ordered embargoed at the wholesale level.

The meeting took place as requested. Mr. Weeden was accompanied by Dr. Peltier and his house counsel, Mr. Simonton, and by Messrs. Corcoran, Foley, Meers, and Lane of counsel.

Dr. Goddard and members of his staff presented the FDA's complaints against the promotional campaign in detail. The record of this meeting reflects that remedial action was accepted by the firm and the following pattern was established:

1. The Commissioner requested full reports as to what Bristol was saying to its detail men about Dynapen.

2. A remedial letter was to be sent airmail to some 280,000 practicing physicians, correcting the faults contained in the Bristol promotional letter.

3. A remedial ad; in this case, a correct ad bearing a legend stating it was to replace a previous ad which the FDA regarded as misleading. It was to be run in the journals where the defective ad appeared.

4. Each remedial form was to include a straightforward scientific statement of the place of Dynapen in therapy.

5. Bristol was to send drafts of proposed remedial actions to FDA by May 29, 1968, for consideration at a meeting with FDA on May 31.

Collateral action was taken to determine how far Bristol's initial campaign had been carried by their detail men. Our inspections of Bristol's plant showed that some 90,000 promotional folders for detail men had been produced. About 30,000 of these had been mailed to the approximately 300 Bristol representatives who were located west of the Mississippi and in Florida. Copies of these folders are being made available for the record—exhibits F and G.

Senator NELSON. They will be printed in the record.

(The information referred to follows:)

EXHIBIT F

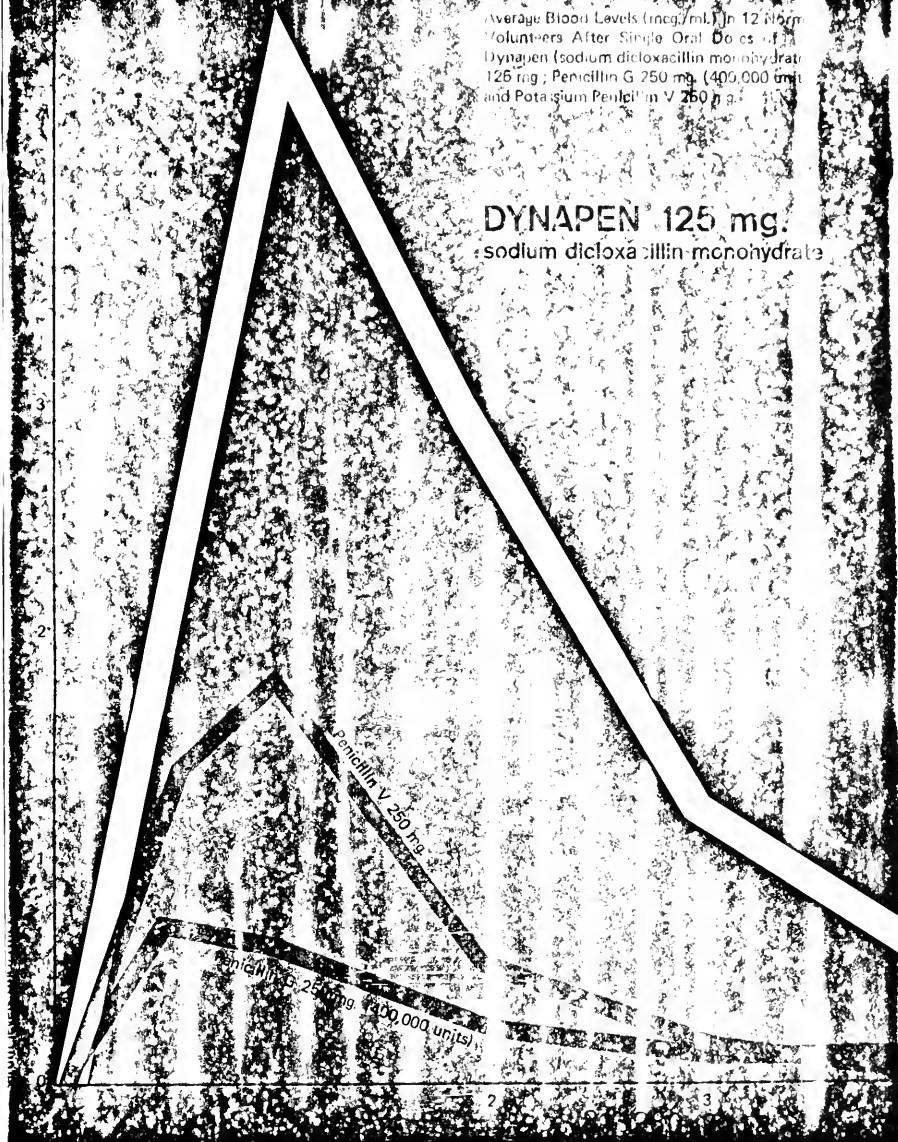
in the hospital
DYNAPEN[®]

(sodium dicloxacillin monohydrate)

a new high potency penicillin
specific for skin/soft tissue infections

Average Blood Levels (mcg./ml.) in 12 Normal
Volunteers After Single Oral Doses of:
Dynamapen (sodium dicloxacillin monohydrate)
125 mg.; Penicillin G 250 mg. (400,000 units)
and Potassium Penicillin V 250 mg.

DYNAPEN® 125 mg.
sodium dicloxacillin monohydrate



ANTIBIOTIC RESISTANCE OF STAPHYLOCOCCI

"For the past decade more and more strains of staphylococci isolated from the community at large have been noted to produce penicillinase. Therefore the distinction as to whether a patient's infection arises in the community or is hospital-acquired no longer serves as a useful guide to choosing antimicrobials with which to initiate treatment."

"During 1967, 76% of staphylococci isolated from in-patients and 53% of strains isolated from out-patients were resistant to penicillin G."

-- Koenig, M. Glenn, "Staphylococcal Infections - Treatment and Control", Diseases of the Month, April 1968, Year Book Medical Publishers Pages 9-10.

"However, the original concept that the penicillinase resistant penicillins should be restricted only to the treatment of proved resistant staphylococcal infections is no longer tenable; delay in the administration of these agents contributes to the high mortality rate in serious infections caused by staphylococci that proved to be resistant."

--New Drugs, 1967 Edition, Page 12.

DYNAPEN[®]

(sodium dicloxacillin monohydrate)

A new high potency penicillin
with outstanding bactericidal performance
in the oral treatment
of hospital infections
due to staphylococci:

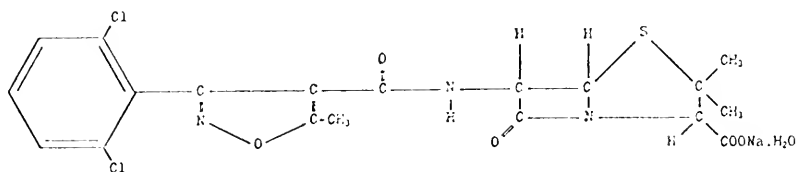
- . post-operative infections
- . trauma complicated by infection
- . burns
- . wounds
- . fractures
- . any skin or soft tissue infection

DYNAPEN^(R)

sodium dicloxacillin monohydrate

DESCRIPTION

DYNAPEN (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazolyl penicillin series. It is the monohydrate sodium salt of 3-(2,6-dichlorophenyl)-5-methyl-4 isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.

SOURCE

Obtained by acylation of 6-aminopenicillanic acid (6-APA) with 2,6 dichlorophenyl and isolated as the sodium salt monohydrate.³

Molecular Formula: $C_{19}H_{16}Cl_2N_3NaO_5S$

CHEMICAL PROPERTIES

Colorless, crystalline solid²

Molecular Weight: 510.3²

Solubility: Greater than 100mg./ml. of water at room temperature.³

Stability: Highly resistant (13 times more so than penicillin G) to inactivation by acid. Also resistant to inactivation by staphylococcal beta-lactamase.^{1,4,5}

Activity Remaining in Per Cent Under Varying Conditions²

Time (days)	Temperature	
	24°C	4°C
2	100	
9	30	
14		90.9

1 mg. of pure sodium salt monohydrate equals 1164 penicillin units;
0.8591 mcg. equals one unit.³

EXCRETION

Renal clearance, about 200 ml. per minute, is considerably less than that of penicillin G which approximates total renal blood flow (500ml. per minute). No detectable accumulation occurs though, even at doses of 250 mg. or 500 mg. every six hours.

TOXICITY

Acute: No deaths in rats, rabbits, or dogs given single oral doses of 8000, 5000, 3000 mg./kg. respectively. LD₅₀ for mice, 8700 mg./kg.
Chronic: No adverse effects in dogs given oral doses as high as 500 mg./kg./day or rats given 1000 mg./kg./day for three months. No deaths occurred in dogs and the same number occurred in treated as in control rats.

PHARMACOLOGY

DYNAPEN (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies¹ with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500 and 1000 mg.^{1,2,3} as measured at the two hour level.

ACTIONS (microbiology)

DYNAPEN (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci. The average Minimal Inhibitory Concentrations (M.I.C.) of DYNAPEN (sodium dicloxacillin monohydrate) for these organisms is as follows:

	Average M.I.C. (mcg./ml.)
Group A beta-hemolytic streptococcus	0.05
Diplococcus pneumoniae	0.10
Staphylococcus (nonpenicillinase-producing)	0.20
Staphylococcus (penicillinase-producing)	0.30

INDICATIONS

The principal indications for DYNAPEN (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

CONTRAINDICATIONS

A history of allergic reactions to penicillins should be considered a contraindication.

PRECAUTIONS

As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteroids, antihistamines).

As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should super infection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time. Safety for use in pregnancy has not been established.

ADVERSE REACTIONS

Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving DYNAPEN (sodium dicloxacillin monohydrate). Pruritus, urticaria, skin rashes, and allergic symptoms have been occasionally encountered, as with all penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilia with or without overt allergic manifestations, has been noted in some patients during therapy.

DOSAGE

For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs) or more;

125 mg. q6h

Children weighing less than 40 Kg. (88 lbs);

12.5 mg./Kg./day in divided doses q.6h

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg. (88 lbs) or more;

250 mg. q6h or higher

Children weighing less than 40 Kg. (88 lbs);

25 mg./Kg./day or higher, in divided doses q.6h

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

SUPPLY

List 78923-DYNAPEN (sodium dicloxacillin monohydrate)

Capsules, 125 mg., bottles of 24

Also available:

List 78566-DYNAPEN (sodium dicloxacillin monohydrate)

For Oral Suspension, 62.5 mg./5ml., 80-ml. bottle

REFERENCES

1. Data on file at Bristol Laboratories.
2. Bennett, J.V., Gravenkemper, C.F., Brodie, J.L., and Kirby, W.M.M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparison with Oxacillin and Cloxacillin." Antimicrobial Agents and Chemotherapy, 1964, pp. 257-262.
3. Naumann, P. and Kemp, E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin." Arzneimittel-Forschung, 15, pp. 139-145, 1965

BRISTOL / Bristol Laboratories
Division of Bristol-Myers Co.
Syracuse, New York 13201

EXHIBIT G

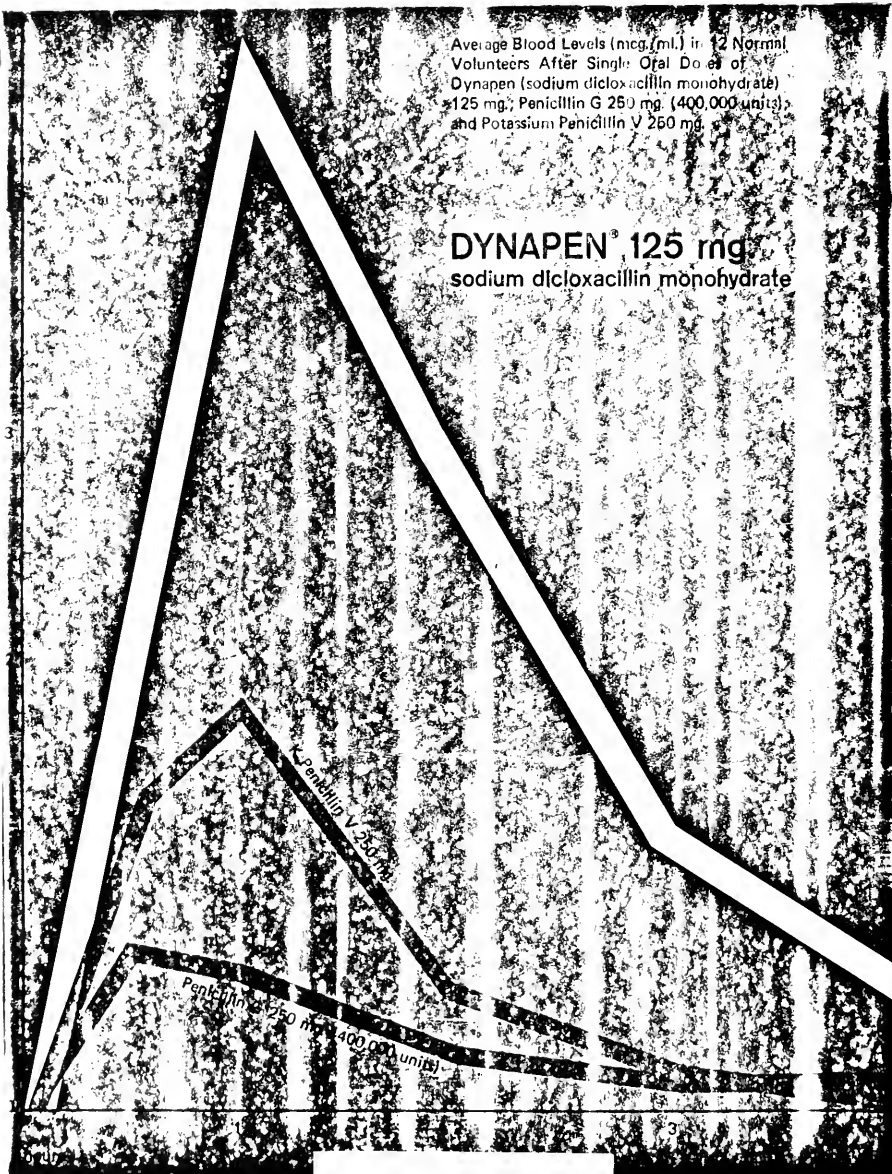
DYNAPEN[®]

(sodium dicloxacillin monohydrate)

**a new high potency penicillin
specific for skin/soft tissue infections**

Average Blood Levels (mcg./ml.) in 12 Normal
Volunteers After Single Oral Doses of
Dynapen (sodium dicloxacillin monohydrate)
125 mg.; Penicillin G 250 mg. (400,000 units)
and Potassium Penicillin V 250 mg.

DYNAPEN® 125 mg
sodium dicloxacillin monohydrate



ANTIBIOTIC RESISTANCE OF STAPHYLOCOCCI

"For the past decade more and more strains of staphylococci isolated from the community at large have been noted to produce penicillinase. Therefore the distinction as to whether a patient's infection arises in the community or is hospital-acquired no longer serves as a useful guide to choosing antimicrobials with which to initiate treatment."

"During 1967, 76% of staphylococci isolated from in-patients and 53% of strains isolated from out-patients were resistant to penicillin G."

-- Koenig, M. Glenn, "Staphylococcal Infections - Treatment and Control", Diseases of the Month, April 1968, Year Book Medical Publishers Pages 9-10.

"However, the original concept that the penicillinase resistant penicillins should be restricted only to the treatment of proved resistant staphylococcal infections is no longer tenable; delay in the administration of these agents contributes to the high mortality rate in serious infections caused by staphylococci that proved to be resistant."

--New Drugs, 1967 Edition, Page 12.

DYNAPEN^(R)

(sodium dicloxacillin monohydrate)

A new high potency penicillin
with outstanding
bactericidal performance in
skin and soft tissue infections
due to staphylococci:

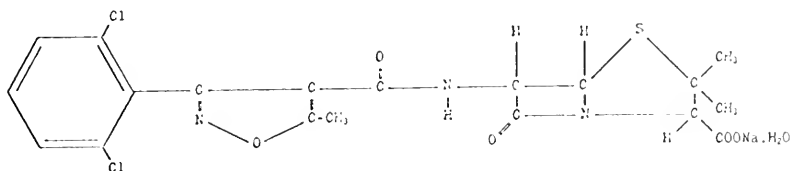
- . pyoderma
- . wounds
- . boils
- . cellulitis
- . lacerations
- . post-operative

DYNAPEN^(R)

sodium dicloxacillin monohydrate

DESCRIPTION

DYNAPEN (sodium dicloxacillin monohydrate) is a new antibacterial agent of the isoxazoly penicillin series. It is the monohydrate sodium salt of 3-(2,6-dichlorophenyl)-5-methyl-4 isoxazoly penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.

SOURCE

Obtained by acylation of 6-aminopenicillanic acid (6-APA) with 2,6 dichlorophenyl and isolated as the sodium salt monohydrate.³

Molecular Formula: $C_{19}H_{16}Cl_2N_3NaO_5S$

CHEMICAL PROPERTIES

Colorless, crystalline solid²

Molecular Weight: 510.3²

Solubility: Greater than 100mg./ml. of water at room temperature.³

Stability: Highly resistant (13 times more so than penicillin G) to inactivation by acid. Also resistant to inactivation by staphylococcal beta-lactamase.^{1,4,5}

Activity Remaining in Per Cent Under Varying Conditions²

Time (days)	Temperature	
	24°C	4°C
2	100	
9	30	
14		90.9

1 mg. of pure sodium salt monohydrate equals 1164 penicillin units;
0.8591 mcg. equals one unit.³

EXCRETION

Renal clearance, about 200 ml. per minute, is considerably less than that of penicillin G which approximates total renal blood flow (500ml. per minute). No detectable accumulation occurs though, even at doses of 250 mg. or 500 mg. every six hours.

TOXICITY

Acute: No deaths in rats, rabbits, or dogs given single oral doses of 8000, 5000, 3000 mg./kg. respectively. LD₅₀ for mice, 8700 mg./kg. Chronic: No adverse effects in dogs given oral doses as high as 500 mg./kg./day or rats given 1000 mg./kg./day for three months. No deaths occurred in dogs and the same number occurred in treated as in control rats.

PHARMACOLOGY

DYNAPEN (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies¹ with an oral dose of 125 mg. gave average serum levels at 60 minutes of 4.74 mcg./ml. At four hours, average levels were 0.62 mcg./ml. The 125 mg. dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500 and 1000 mg.^{1,2,3} as measured at the two hour level.

ACTIONS (microbiology)

DYNAPEN (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci. The average Minimal Inhibitory Concentrations (M.I.C.'s) of DYNAPEN (sodium dicloxacillin monohydrate) for these organisms is as follows:

	Average M.I.C. (mcg./ml.)
Group A beta-hemolytic streptococcus	0.05
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Staphylococcus (nonpenicillinase-producing)	0.20
Staphylococcus (penicillinase-producing)	0.30

INDICATIONS

The principal indications for DYNAPEN (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of those infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

CONTRAINDICATIONS

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PRECAUTIONS

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As with other agents capable of altering flora, the possibility of superinfection with mycotic organisms or other pathogens exists during the periods of use of this drug. Should super infection occur, appropriate treatment should be initiated and discontinuation of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time. Safety for use in pregnancy has not been established.

ADVERSE REACTIONS

Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving DYNAPEN (sodium dicloxacillin monohydrate). Pruritus, urticaria, skin rashes, and allergic symptoms have been occasionally encountered, as with all penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

DOSAGE

For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg. (88 lbs) or more;

125 mg. q6h

Children weighing less than 40 Kg. (88 lbs);

12.5 mg./Kg./day in divided doses q.6h

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg. (88 lbs) or more;

250 mg. q6h or higher

Children weighing less than 40 Kg. (88 lbs);

25 mg./Kg./day or higher, in divided doses q.6h

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

SUPPLY

List 78923-DYNAPEN (sodium dicloxacillin monohydrate)

Capsules, 125 mg., bottles of 24

Also available:

List 78566-DYNAPEN (sodium dicloxacillin monohydrate)

For Oral Suspension, 62.5 mg./5ml., 80-ml. bottle

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2. Bennett, J.V., Gravenkemper, C.F., Brodie, J.L., and Kirby, W.M.M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparison with Oxacillin and Cloxacillin." Antimicrobial Agents and Chemotherapy, 1964, pp. 257-262.
3. Naumann, P. and Kemp, E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin." Arzneimittelforschung, 15, pp. 139-145, 1965

/BRISTOL/ Bristol Laboratories
Division of Bristol-Myers Co.
Syracuse, New York 13201

Dr. MINCHEW. Mr. Chairman, I am sure that your committee will see quickly that the detail men's message to physicians was similar to that in the company's promotional letter and journal ads.

It was found that about 64,000 packages of 24 capsules of Dynapen had been distributed, about 42,000 units to retail pharmacies and about 3,500 units to hospitals.

Because of the large amount of material shipped, it was decided to request recall of the goods to a level of control of the firm.

Senator NELSON. What did that mean, physically?

Mr. GOODRICH. That meant getting it back either in their own warehouse or in the case of materials that was in drugstores the company was required to send a telegram to all the druggists to the effect it would be illegal to fill a prescription with that product until the matter was clarified.

Senator NELSON. And how long did it take for clarification to occur?

Mr. GOODRICH. Clarification took until June 21, when the corrective ad ran in the Medical World News.

Senator NELSON. And how long was it withheld from the market then?

Mr. GOODRICH. From May the 24th, when Dr. Goddard sent them a telegram canceling the certificates, until June 21, when the corrective ad appeared in Medical World News.

Senator NELSON. I want to commend the FDA for this action. I think it is strong and dramatic and the proper thing to do, and I am confident if you continue with this kind of action each time they intentionally violate the regulations that have been established, that it will have some impact, because I think it would appear that the only effective way is to do something dramatic enough to not only protect the public but to make it expensive for them to engage in this kind of activity.

It seems to me in the past frequently it wasn't sufficient penalty to their violation of the FDA regulations. If the penalty is made tough enough every single time, it may very well work. So I think the FDA is to be commended for this very strong action.

Dr. MINCHEW. Prior to meeting with the firm on May 31, 1968, the FDA prepared guidelines for the remedial letter. At this meeting Bristol was told that their proposed remedial letter was promotional, not adequately corrective, and unsatisfactory. Composition of the remedial ad was settled.

Bristol agreed at this meeting to notify its detail men not to use the promotional folder and to use only the approved package labeling for detailing Dynapen. The firm agreed to "freeze" stocks of Dynapen through a letter addressed to wholesalers and a letter to all retail accounts. The letters were to state the reason for the "freeze." Copies of these communications are being included for the record—exhibits H, I, and J.

Senator NELSON. They will be included in the record.

(The information referred to follows:)

EXHIBIT H

BRISTOL LABORATORIES,
Syracuse, N.Y., June 3, 1968.

REQUEST FOR EMBARGO OF DYNAPEN®

DEAR PHARMACISTS: The Food and Drug Administration has questioned the journal advertising and introductory letter to physicians used by Bristol Laboratories in announcing the marketing of Dynapen (sodium dicloxacillin monohydrate). For this reason the Food and Drug Administration has revoked the release of all lots distributed and further distribution of the product or the use of it in filling prescriptions, at this time, would be illegal.

Accordingly, until further notice, we request that all supplies of Dynapen be held and not shipped, sold or dispensed.

We will notify you as soon as this material can be released.

Thank you.

Sincerely yours,

LORNE MACBETH,
General Sales Manager.

EXHIBIT I

BRISTOL LABORATORIES,
Syracuse, N.Y., June 3, 1968.

Important Notice to all Bristol Wholesalers:

REQUEST FOR EMBARGO OF DYNAPEN®

The Food and Drug Administration has questioned the journal advertising and introductory letter to physicians used by Bristol Laboratories in announcing the marketing of Dynapen (sodium dicloxacillin monohydrate). For this reason the Food and Drug Administration has revoked the release of all lots distributed and further distribution of the product or the use of it in filling prescriptions, at this time, would be illegal.

Accordingly, until further notice, we request that all supplies of Dynapen be held and not shipped, sold or dispensed.

We will notify you as soon as this material can be released.

Thank you.

Sincerely yours,

LORNE MACBETH,
General Sales Manager.

EXHIBIT J

BRISTOL LABORATORIES,
Syracuse, N.Y., June 3, 1968.

REQUEST FOR EMBARGO OF DYNAPEN®

DEAR HOSPITAL PHARMACIST: The Food and Drug Administration has questioned the journal advertising and introductory letter to physicians used by Bristol Laboratories in announcing the marketing of Dynapen (sodium dicloxacillin monohydrate). For this reason the Food and Drug Administration has revoked the release of all lots distributed and further distribution of the product or the use of it in filling prescriptions, at this time, would be illegal.

Accordingly, until further notice, we request that all supplies of Dynapen be held and not shipped, sold or dispensed.

We will notify you as soon as this material can be released.

Thank you.

Sincerely yours,

LORNE MACBETH,
General Sales Manager.

Dr. MINCHEW. Another meeting was set for Monday, June 3, 1968, to finalize remedial actions previously discussed. At this meeting, the contents of the remedial letter and correct ad were agreed upon. Bris-

tol was advised that recertification could be effected only after the remedial ad had appeared in the same journals as the original ad.

The events following these decisions are reflected in the remedial letter and the correct ads, copies of which are included for the record—exhibits K and L.

Senator NELSON. They will be included in the record.

(The information referred to follows:)

EXHIBIT K

BRISTOL LABORATORIES,
Syracuse, N.Y.

DEAR DOCTOR: The Food and Drug Administration has asked that we call your attention to our letter of May 17, 1968 which announced the coming availability of Dynapen (sodium dicloxacillin monohydrate). The Food and Drug Administration has expressed concern that our discussion of this drug in terms of treating skin and soft tissue infections created misleading impressions concerning the proper use of Dynapen in its limited appropriate indications.

Therefore, we wish to specify the indications and limitations for use of this drug in detail as follows:

1. The principal indication for Dynapen is in the treatment of infections known to be due to penicillinase-producing staphylococci which have been shown to be sensitive to it.

2. If antibiotic therapy is considered necessary in potentially serious infections while awaiting reports of cultures and sensitivity studies, Dynapen may be used to initiate therapy in such patients in whom a penicillinase-producing staphylococcus is suspected. (See Important Note below.)

Important Note

Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When it is judged important that treatment be initiated before definitive culture and sensitivity results are known the choice of Dynapen should take into consideration the knowledge that its has also been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci and penicillin G-sensitive staphylococci. In serious, life threatening infections oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

Methicillin, a compound working through a similar mechanism against penicillin G-resistant staphylococci, has been available for nine years. It is a fact that strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. It has been demonstrated that such strains are almost always resistant to other penicillinase-resistant penicillins, such as the isoxazole group of which Dynapen is a member. When such a strain is isolated, use of routine antibiotic discs cannot be relied on to differentiate relative sensitivity. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, the Food and Drug Administration is concerned that widespread use of the penicillinase-resistant penicillins in infections other than those due to penicillin G-resistant staphylococci may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Therefore, if the bacteriology report indicates the infection is not due to a penicillin G-resistant staphylococcus, the physician is advised to continue therapy with a drug other than Dynapen or any other penicillinase-resistant semi-synthetic penicillin.

Indicated surgical procedures should be performed.

Contraindications

A history of allergic reactions to penicillin should be considered a contraindication.

Information in our announcement letter, or that you may have received from one of our sales representatives, should be carefully considered in light of the preceding clarification.

We have discontinued the advertising in question. Future advertising will be appropriately modified. The drug is not available for prescription at this time. We will notify you when it becomes available.

Sincerely,

H. C. PELTIER, M.D.,
Vice President, Medical Director.

EXHIBIT L

NEW TYPE OF DRUG
 IN "DYNAPEN"
 NEW TYPE OF DRUG
 IN "DYNAPEN"
 NEW TYPE OF DRUG
 IN "DYNAPEN"
 NEW TYPE OF DRUG
 IN "DYNAPEN"
 NEW TYPE OF DRUG
 IN "DYNAPEN"

Dynapen is barbiturate
 Dynapen is an effective analgesic
 Dynapen is highly effective against pain
 Dynapen is not habit-forming

Now available

TM
 Dynapen

Published to replace a previous
 in this space which the Food & Drug
 Administration considered to
 misleading impressions concern
 proper use of Dynapen.

TEXT OF OFFICIAL PACKAGE CIRCULAR FOR DYNAPEN

Description: DYNAPEN (sodium dicloxacillin monohydrate) is a new antibiotic, a member of the isoxazolyl penicillin series. It is the monohydrate of sodium salt of 6-(2,6-dichlorophenyl)-5-methyl-3-oxo-4-isoxazolyl penicillin. The drug resists destruction by the enzyme penicillinase (beta-lactamase). It has been demonstrated to be especially efficacious in the treatment of penicillinase-producing staphylococcal infections and effective in the treatment of other commonly encountered Gram-positive coccal infections.

Pharmacology: DYNAPEN (sodium dicloxacillin monohydrate) is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of dicloxacillin gives blood levels considerably in excess of those attained with equivalent doses of any other presently available oral penicillin. The levels are comparable to those achieved with intramuscular administration of similar doses of penicillin G. Studies¹ with an oral dose of 125 mg gave average serum levels at 60 minutes of 4.74 mcg/ml. At four hours, average levels were 0.52 mcg/ml. The 125 mg dose gave peak blood levels 5 times higher than those of 250 mg. of penicillin G and 2 to 4 times higher than those of 250 mg. of potassium phenoxymethyl penicillin. Serum levels after oral administration are directly proportional to dosage at unit doses of 125, 250, 500, and 1000 mg.^{1,2,3} as measured at the two-hour level.

Actions (Microbiology): DYNAPEN (sodium dicloxacillin monohydrate) is active against most Gram-positive cocci including beta-hemolytic streptococci, pneumococci, and sensitive staphylococci. Because of its resistance to the enzyme penicillinase, it is active against penicillinase-producing staphylococci.

The average Minimal Inhibitory Concentrations (M.I.C.'s) of DYNAPEN (sodium dicloxacillin monohydrate) for these organisms are as follows:

	Average M.I.C. (mcg./ml.)
Group A beta-hemolytic streptococcus	0.05
Diplococcus pneumoniae	0.10
Staphylococcus (nonpenicillinase-producing)	0.20
Staphylococcus (penicillinase-producing)	0.30

Indications: The principal indications for DYNAPEN (sodium dicloxacillin monohydrate) are in the treatment of infections known to be due to penicillinase-producing staphylococci and in instituting treatment of these infections where a penicillinase-producing staphylococcus is suspected.

Bacteriologic studies to determine the sensitive organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is sensitive to penicillin G, the physician is advised to use penicillin G or phenoxymethyl penicillin (penicillin V), penicillinase-resistant or appropriate antibiotic therapy because of the appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and nonpenicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

Indicated surgical procedures should be performed.

Contraindications: A history of allergic reactions to penicillins should be considered a contraindication.

Precautions: As with any penicillin, a careful inquiry about sensitivity or allergic reactions to penicillin or other antigens should be made before the drug is prescribed. Allergic reactions are more likely to occur in hypersensitive individuals. Should an allergic reaction occur during therapy, the drug should be discontinued and the patient treated with the usual agents (epinephrine, corticosteroids, antihistamines).

As with other penicillins, risk of altering flora, the possibility of superinfection with mycotic organisms or other pathogenic agents during the period of use of this drug. Should superinfection occur, appropriate treatment should be instituted and discontinuance of dicloxacillin therapy should be considered.

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic systems, is strongly recommended.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Safety for use in pregnancy has not been established.

Adverse Reactions: Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving DYNAPEN (sodium dicloxacillin monohydrate). Pruritus, urticaria, skin rashes, and allergic symptoms have been occasionally encountered, as with all penicillins. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pretherapeutic determinations were not made. Minor changes in the results of cephalin flocculation tests have been noted without other evidence of hepatic dysfunction. Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy.

Dosage: For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 Kg (88 lbs) or more: 125 mg q 6h.

Children weighing less than 40 Kg (88 lbs): 12.5 mg/Kg/day in divided doses q 6h.

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 Kg (88 lbs) or more: 250 mg. q 6h. or higher.

Children weighing less than 40 Kg (88 lbs): 25 mg/Kg/day, or higher, in divided doses q 6h.

Experience in the neonatal period is limited. Therefore, a dose for the newborn is not recommended at this time.

Studies indicate that this material is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

M.R.I.: Infections caused by Group A beta-hemolytic streptococci should be treated for at least 10 days to help prevent the occurrence of acute rheumatic fever or acute glomerulonephritis.

Supply:

List 78923—DYNAPEN (sodium dicloxacillin monohydrate) Capsules, 125 mg., bottles of 24.

Also available:

List 78565—Oral Suspension, 62.5 mg./5 ml., 80 ml. bottle

References: 1. Data on file at Bristol Laboratories. 2. Bennett, J. V., Gravenkemper, C. F., Brodie, J. L., and Kirby, W. M. M., "Dicloxacillin, a New Antibiotic: Clinical Studies and Laboratory Comparisons with Oxacillin and Cloxacillin." *Antimicrobial Agents and Chemotherapy*, 1964, pp. 257-262. 3. Naumann, P. and Kempf, E., "Dicloxacillin, a New Acid and Penicillinase Stable Oral Penicillin." *Arzneimittel-Forschung*, 15, pp. 138-145, 1965.

Bristol Tel. phone Service: (315) 437-0569. If you have any question relating to the use of DYNAPEN (sodium dicloxacillin monohydrate) or any other Bristol product, please call this number collect. A physician in the Medical Department of Bristol Laboratories will be available to answer your question.



Bristol Laboratories
Division of Bristol-Myers Co.
Syracuse, New York 13201

Dr. MINCHEW. We instituted recertification of Dynapen as of June 21, 1968.

Mr. Chairman, if you have any questions, my associates and I will attempt to answer them.

Mr. GORDON. Mr. Chairman, may I interrupt here? The subcommittee has secured documents taken from the files of the Food and Drug Administration that pertain to this matter, and I ask that they be included in the record at the appropriate place.

Senator NELSON. Without objection.

Could you comment—and I commend the FDA for its prompt action on Dynapen—is there any explanation why some 6 weeks elapsed between the faulty promotion of Vibramycin detailing at a medical meeting, and your contact with the manufacturer to request corrective steps?

Dr. MINCHEW. It certainly takes an additional amount of time to obtain the proper type of documentation when we are dealing with action over oral detailing. In the case of the Vibramycin, the problem was in obtaining affidavits and having the adequate legal documentation to support our action.

The situation with the Dynapen was that the errors were written errors in promotional labeling and journal advertising over which we felt that immediate action could be supported.

Senator NELSON. So you acted as expeditiously as you could in the Vibramycin case. You simply didn't have the documents in hand to support action until you secured affidavits and so forth, is that correct?

Dr. MINCHEW. I believe we did, unless Mr. Goodrich has—

Senator NELSON. Excuse me, did you have some questions?

Mr. GROSSMAN. A couple of questions. First, in looking over the various cases in the last several days, I wondered if you feel that there is some type of consistency in policing activities of advertising? In other words, do you feel that the action you are taking in these cases is consistent with the degree of risk, or how is it decided what action you are going to take? Perhaps Mr. Goodrich would wish to respond as to the legal point of view.

Mr. GOODRICH. We have decided in each case on the basis of an examination of the ad and the company's performance on whether or not a remedial letter would be required. This has been taken up in each instance at the Commissioner level. Dr. Goddard initiated it. Dr. Ley has continued it.

The practice has been for the Division of Medical Advertising and the Director of the Bureau of Medicine, when they encounter an advertisement that they regard as particularly offensive, to call that to the Commissioner's attention.

Part of our program has been to pay special attention to the initial campaign for the launching of a new product. We advised this committee of that some time ago, and we followed through on it.

This has been important to make sure that the drugs are initially introduced to the profession on the basis on which they were approved. That is what led us into the Vibramycin, Dynapen episodes.

Now in the case of Dynapen, we felt that because we had a long and protracted discussion with the company, because we felt we had a clear understanding with them about the conditions of appropriate use, and because of the initial launching of the product completely at

variance with what we thought we had agreed upon, we concluded. Dr. Goddard and the others, that these steps, certification cancellation, withdrawing the drug and remedial letters were the most appropriate. This was the first instance for a remedial ad.

Mr. GROSSMAN. In this same area on page 4 of Dr. Minchew's prepared statement, he is talking about Tegopen. He said, "In October, we publicly criticized this ad campaign as offering the drug for conditions which it had not been approved."

What does he mean by "publicly criticized"?

Mr. GOODRICH. We met on October 20, 1966, before the Pharmaceutical Advertising Club in New York to discuss on a broad basis the FDA's requirements and the industry's performance in complying with advertising regulations.

I personally took up the eight products that had been introduced in the previous year, and that had achieved rank among the 200 most prescribed.

Tegopen was one of those drugs. We presented to the group, including Bristol and its people who were there, photographs of the advertising campaign and our criticism of it. Essentially, it was that the Tegopen was characterized as an everyday penicillin. The visuals on the ads showed physicians using it at, as I remember it, 10:01, 10:08, 10:14 a.m., and so forth, in patients, which would mean routine practice.

We then said that our understanding was that the product had been approved for a special purpose and not as an "everyday" penicillin. Bristol came to see us within a very few days, as our statement indicates, saying: "We think that Tegopen is indeed an everyday penicillin," and that is when we told them that they would have to get approval for such a purpose.

Mr. GROSSMAN. May I ask you, do you think this is the normal procedure? In other words, would you consider this a normal procedure to criticize, to make a statement publicly without contacting the firm first and/or trying to stop the promotion by the firm?

Mr. GOODRICH. We considered it an invitation by the pharmaceutical advertising group, as a whole, and the companies, to meet with us and discuss on a broad basis what it was we expected in advertising, and what we thought of the existing practices.

Now we haven't had another meeting of that kind. I didn't initiate the invitation. It was initiated by someone else. We simply participated.

In other words, to get this matter of prescription drug advertising corrected, this offered us an opportunity to talk both with the companies, with advertising agencies, and with their creative people. We thought we talked with them on a level that was fully understood.

Mr. GROSSMAN. It just seems to me if there is improper advertising in any case like this, by one particular firm, that the option of FDA would not be to go to a forum and publicly discuss it, but would rather be to go to Bristol and tell them, "You do this or you do this or we are going to stop the distribution of the drug."

Mr. GOODRICH. As the facts show, this has been our practice since that time. It became important in October 1966 to communicate with the entire industry and with their advertisers and the others concerned.

Mr. GROSSMAN. One other point.

Senator NELSON. May I interrupt? Was that a public meeting?

Mr. GOODRICH. Yes, sir.

Mr. GROSSMAN. One other point. On page 3, and this is involved a little bit with a different problem, I wonder how effective your warnings are to the doctor. We have talked about the other aspects of advertising. I don't know, maybe a doctor looks at words differently than I do as a lawyer. But I notice that it says on page 3, one of the warnings recommended would be, "If it is determined that the infection is not due to a penicillin G resistant staphylococcus, a change to penicillin G or phenethicillin may be considered."

Now as a doctor, do I react very violently when I see, "May be considered"?

Mr. GOODRICH. I think you react properly. We have, in the Dynapen letters, and in the promotional revisions that are now underway, expressed that more positively.

Mr. GROSSMAN. One final point, if I may. Senator Hatfield can't be here this morning. He has another hearing. Yesterday I think he and Dr. McCleery were discussing this point of how long and what action was taken with Vibramycin on the visual aids. I would like to ask that two letters be included in the record.

One is a letter from Chas. A. Pfizer to Dr. McCleery, dated October 6, and one is dated October 23, signed by Dr. Minchew, relating to the fact that the FDA did in fact say that the visual aids could be used for 1 month's time. I think you agreed to that. Thank you.

(The letters follow:)

CHAS. PFIZER & Co., INC.
October 6, 1967.

Re Vibramycin.

R. S. MCCLEERY, M.D.,

Director, Division of Medical Advertising, Bureau of Medicine, Food and Drug Administration, Washington, D.C.

DEAR DR. MCCLEERY: We refer you to your meetings with Mr. Alterno and Dr. Trout on September 5 and September 6, 1967 in regard to Vibramycin.

As a result of these meetings Dr. Ley gave us permission to use the existing Vibramycin visual aid and compendium for a period of one month from the date of approval (September 14, 1967) and we were then to replace that visual with the new revised visual aid.

During the coming week of October 9, 1967 the new visual aids will be sent to our sales force. Upon receipt of the revised visual aid the detailman will return his copy to his District Manager and will sign a return sheet. The visual aid, along with the compendium, will then be returned to the company where they will be destroyed.

Sincerely yours,

M. G. ADAIR,
FDA Liaison Department.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., October 23, 1967.

"Vibramycin Suspension"—NDA 50-006

"Vibramycin Capsules"—NDA 50-007

Re Vibramycin—148z.3 and 148z.4.

CHAS. PFIZER & Co., INC.,
New York, N.Y.

(Attention: Mr. M. G. Adair)

GENTLEMEN: We have no objection to the Vibramycin visual aid (P159x67R1—Issued October 1967) submitted with your letter of October 6, 1967, nor to the manner in which you propose to dispose of copies of the previous visual aid and compendium.

The draft of the compendium submitted with your letter of October 2, 1967 is satisfactory.

Sincerely yours,

B. H. MINCHEW,
HERBERT L. LEY, Jr., M.D.,
Director, Bureau of Medicine.

Senator NELSON. I want to thank you very much for your presentation this morning. Our next hearing will be on Wednesday at 10 a.m. The witness will be Dr. Philip Lee, Assistant Secretary of HEW, and staff, to discuss the HEW Task Force Report on Prescription Drugs.

Thank you very much.

(Whereupon, at 10:45 a.m., the committee adjourned until Wednesday, September 25, 1968, at 10 a.m.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, SEPTEMBER 25, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:15 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. The witness this morning is Dr. Philip R. Lee, Assistant Secretary for Health and Scientific Affairs of the U.S. Department of Health, Education, and Welfare.

Dr. Lee, we appreciate your taking the time to come over here and testify this morning. Your testimony will be on the Report of the Task Force on Prescription Drugs. You may present your statement in any way you wish. If you wish to elaborate on it you may, or you may depart from it.

STATEMENT OF DR. PHILIP R. LEE, ASSISTANT SECRETARY, OFFICE OF HEALTH AND SCIENTIFIC AFFAIRS, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE; ACCOMPANIED BY DR. MARK NOVITCH, OFFICE OF HEALTH AND SCIENTIFIC AFFAIRS, HEW; MILTON SILVERMAN, PH. D., OFFICE OF HEALTH AND SCIENTIFIC AFFAIRS, HEW; AND WILLIAM W. GOODRICH, GENERAL COUNSEL, FOOD AND DRUG ADMINISTRATION, HEW

Dr. LEE. Thank you, Mr. Chairman.

I am accompanied by Mr. William Goodrich on my right, Assistant General Counsel; on my immediate left by Dr. Milton Silverman and on his left, Dr. Mark Novitch, both members of my staff in the Office of Health and Scientific Affairs. Dr. Silverman and Dr. Novitch have been two of the key staff members on the Task Force on Prescription Drugs.

Just over a year ago, former Secretary Gardner established a special Task Force on Prescription Drugs, asking that we thoroughly examine the problems of covering the costs of out-of-hospital prescription drugs under medicare. We were not bound to recommend for or against any specific program or approach. Rather, our directive was first to investigate and then to make whatever recommendations we found to be appropriate.

The Secretary—like many others—recognized the enormous complexity of this assignment. Some answers, he felt, might be found speedily, and this has turned out to be true. Others, he predicted, might take many months or even years of work, and this, too, was an accurate forecast.

The task force still has not completed the detailed studies on program financing, administrative procedures, reimbursement methods, and utilization review, all of which are essential to a final determination. When this material has been analyzed, we shall be in a position to submit our final report, which we expect to be completed before the end of 1968.

We have made two interim reports, however. The first was submitted to the Secretary in March of this year. In it, we recommended legislation to establish reasonable cost and charge ranges for drugs supplied in federally supported health programs. We also recommended legislation to authorize publication of a Federal drug compendium.

A second interim report, much broader in scope, was released earlier this month. Today, Mr. Chairman, I am pleased to submit a copy of the report for the record and to have this opportunity to discuss portions of it in somewhat more detail.

Senator NELSON. You are referring to the task force's second interim report on August 30, 1968?

Dr. LEE. Yes.

Senator NELSON. That report will be printed in full in the record.¹

Dr. LEE. Thank you very much, Mr. Chairman.

In fulfilling its mission, the task force has been confronted with many of the same problems which have been considered in the exhaustive and informative hearings conducted during the past year or more by your distinguished subcommittee.

You have demonstrated a keen interest in drug research, drug patents, drug promotion, and drug prices. The task force has also examined these problems.

You have demonstrated interest in the prescribing habits of physicians. The task force has reviewed this as well.

You have been interested in drug quality, and in the confused problems of chemical equivalents and clinical equivalents. So has the task force.

And—of most importance—we share the conviction, I am sure, that the major goal of our efforts must be to improve the quality of health care provided to all Americans.

This was stressed last year by Secretary Gardner, when he established the task force upon a directive from the President. The Secretary said:

In all of its work, I have asked the task force to measure the value of possible solutions not only in terms of dollars to be saved, but in the quality of health care to be delivered.

Before discussing our recent report, Mr. Chairman, I feel it is important to note that even before the task force embarked on its mission, it was evident that we would need a tremendous amount of basic, objective information on drugs—on their development, production,

¹ See report beginning at p. 3737, *infra*.

distribution, prescription, costs and uses. And at the start, we found that much of the information we urgently needed simply was not available.

This lack of scientific data was clearly responsible for much of the controversy which has characterized this entire area. For example, on the warmly disputed matter of "generic equivalents," it was all too obvious that much of the controversy was due to the fact that we didn't have the facts. We had to go out and get them—to go into the laboratories and clinics, and carry out the necessary scientific research.

Senator NELSON. I might say, Dr. Lee, as I have read over the past year and a half the publications issued by the Pharmaceutical Manufacturers Association, I have noted that they made assertions that would make it appear to the physician that they had the facts, which they obviously did not have, on this issue. Please continue.

Dr. LEE. In this and other phases of the task force's operations, I feel it is also important to emphasize the invaluable assistance we have received from virtually all of the groups and associations and scientific communities involved. More than 200 of the Nation's experts in this area have given freely of their time to provide us with the benefit of their advice and counsel. Leaders of the drug industry have offered us a wealth of previously unavailable information.

The task force has assembled a great deal of material which should be made widely available to Congress, to Government agencies, to the drug industry, to the medical profession, to health insurance groups, to consumer groups, and others. This information will be made available in a series of background papers. The first, about the health needs and resources of the elderly, and their actual use of prescription drugs, will be published very shortly. Others will follow quickly thereafter.

Time will not permit even a brief discussion of all the findings and recommendations we have presented to date. Three areas may be of particular interest to your subcommittee—first, the prescribing patterns of physicians and the sources of information on which these patterns are based; second, the promotional activities of drug manufacturers; and third, drug quality and the equivalency of generic name products.

Clearly, Mr. Chairman, the key figure in establishing patterns of drug use is the prescribing physician. Because these patterns are so central to the success of a medicare drug insurance program, the task force has looked carefully at the process of decisionmaking in drug therapy.

It is not a simple process. Each time a course of therapy is selected, the well-trained and conscientious physician must try to answer such questions as:

Which is the best drug for the problem at hand?

Which is the most appropriate dosage form?

What are the optimal amounts and duration of therapy?

What side effects, if any, must be anticipated?

Is some condition present which would rule out the use of this drug?

Is the patient taking another drug with which this one is incompatible?

Under the best of circumstances, judgments on these and similar questions are difficult, and their difficulty as well as their importance, Mr. Chairman, cannot be overstated.

This is why we are devoting a major effort to the review of claims for all drugs approved through the new drug procedures of FDA between 1938 and 1962. If the labeling claims are not supported by substantial evidence, the prescriber is misled as to the effectiveness that may be expected.

This is also why we are trying to improve the adverse reaction experience reporting systems available to the FDA.

Senator NELSON. You are saying you are reviewing the labeling claims made on the new drugs between 1938 and 1962; is that right?

Dr. LEE. Yes, sir.

Senator NELSON. And you have the authority under the 1962 law, I understand, to control the labeling on those drugs?

Dr. LEE. Right.

Senator NELSON. Can you advise the committee how far along you are in a review of the claims made for these drugs?

Dr. LEE. As you know, this study was initiated with the National Academy of Sciences—National Research Council, to review the efficacy of approximately 3,000 drugs. About half of these have been completed and submitted to the Food and Drug Administration.

Based on the review by panels of scientists in each of the drug areas, the Food and Drug Administration is now determining what actions it is appropriate to take under individual circumstances. There are several different categories. And these are being evaluated, of course, in terms of their effectiveness. Safety is not at issue, because that was a requirement prior to 1962.

Senator NELSON. How many have been reviewed of the 3,000?

Dr. LEE. About how many? About half. Mr. Goodrich can give us more detail.

Mr. GOODRICH. About half of the reports have been received by the Food and Drug Administration from the Academy. Dr. Lee establish a task force to deal with those reports. About 10 percent of what we have received have been processed through that task group.

Announcements have been made in the Federal Register of the status of about half of those drugs. In short, we are just starting the announcements of the results of the Academy review and our implementation steps which Dr. Lee was about to discuss in terms of the various categorizations of these drugs.

Dr. LEE. The drugs have been categorized, Mr. Chairman, as ineffective, possibly effective, probably effective, effective but—in other words, requiring some change in the labeling—and those that are effective and require really no change in labeling.

Senator NELSON. Have you released any information on the 1,500 as to those which are ineffective, those which are probably ineffective, and so forth?

Dr. LEE. On a limited number. Mr. Goodrich can give you that information.

Mr. GOODRICH. Yes, we have. This has been done on a product basis as we receive the reports back. The first announcement was on a citrus bioflavonoid product on which the announcement was that the product was ineffective.

We gave notice of a proposal to withdraw the product from the market. The companies are resisting both at the administrative level and by suing us in the court in Alexandria for a declaratory judg-

ment to the effect that we haven't any right to examine the effectiveness of this class of drugs.

Senator NELSON. This is a prescription drug?

Mr. GOODRICH. No.

Senator NELSON. And they are contesting the legal authority of the FDA to act in this?

Mr. GOODRICH. Yes.

Let me go back. It is an over-the-counter drug for so-called capillary fragility, for bleeding states. The contention is that since the product became generally recognized as safe some years ago—it is essentially innocuous—that it is not subject to have the effectiveness review that is now going on. We, of course, are contesting that issue in the district court in Alexandria.

Senator NELSON. Under the law, if the drug is one of that class of drugs involved here and is found to be ineffective, does FDA have the authority to require its removal from the marketplace?

Mr. GOODRICH. We think so. The drug industry is contending in a suit that has been pending in Wilmington, Del., since soon after the enactment of the 1962 amendments that they have certain protections under the grandfather clause of the 1962 amendments. That case has never been pressed on to trial because of the pendency of the NAS-NRC review, and the plaintiff has been reporting to the court that it wishes to await further process in that review before deciding what to do about that pending action in Wilmington.

Senator NELSON. The National Academy is doing the review?

Mr. GOODRICH. Yes.

Senator NELSON. And they, I assume, are using consulting clinicians around the country?

Dr. LEE. Yes, sir, the Academy set up a number of panels with a chairman of each panel. They review all the data that is available, evaluate it and make their recommendations.

Senator NELSON. And on this drug they came to the conclusion it was ineffective?

Mr. GOODRICH. Yes.

Senator NELSON. Is the company contesting that conclusion?

Mr. GOODRICH. No, they are contesting our right to subject the article to administrative procedures of requiring proof of effectiveness. They would, of course, I think contend that they have some evidence that the product is effective. They have submitted that evidence to the Food and Drug Administration, and it has been reviewed and found to be wholly inadequate.

Senator NELSON. So what they would like is a chance to sell placebos at high prices?

Mr. GOODRICH. Right.

Senator NELSON. Please go ahead.

Dr. LEE. To return to my statement, Mr. Chairman, and to focus on the adverse drug reaction reporting system available to the Food and Drug Administration, we are trying to improve this system. And I would just like to cite a recent example in an article which revealed that among a group of patients hospitalized for chronic illness, 35 percent had at least one reported adverse drug reaction. Eighty percent of these reactions were either moderate or major in their severity. Only 20 percent were described as minor.

Some drug reactions are unpredictable and often have more to do with an unusual patient response than with any common side effect of the drug. Others, while predictable, are quite probably regarded as an acceptable risk in obtaining an important therapeutic effect. But many adverse reactions are needless, especially when an agent of serious potential toxicity is used in the treatment of a relatively minor illness.

The lesson of this and similar studies is clear, Mr. Chairman. The rational use of today's increasingly potent drugs requires not only continuous access to current, objective, and accurate drug information during the years of practice, but also a thorough medical school grounding in the principles of drug therapy. The task force strongly supports improvement in both of these areas.

Senator NELSON. You state that the rational use of today's increasingly potent drugs requires continuous access to current, objective and accurate drug information. Is there wide access on the part of the medical community now to objective, accurate drug information on all drugs?

Dr. LEE. No, I don't believe it is adequate, Mr. Chairman. If a physician wishes to seek out the information, he can obtain it. But there are a variety of sources that he must use, beginning with a textbook of pharmacology. There are textbooks on current drug therapy which usually are published every year or two, or brought up to date every year or two. The articles, of course, are prepared many months in advance of publication, so that it may mean that for a particular disease area the description is 1 or 2 or more years old.

He requires current information like the Medical Letter, which relatively few physicians subscribe to. The physician also requires information which we think can best be made available in a drug compendium. In other words, information on all the drugs that are available—factual, accurate information.

And this simply isn't available to the physician today, as Mr. Goodrich pointed out, except in the package insert provided with the individual drug. When a physician wishes to compare the effectiveness and side effects of one drug with other drugs he must go to the individual package inserts to get that kind of detailed information.

Senator NELSON. But does the doctor always have the package inserts?

Dr. LEE. No, sir, he rarely has them.

Senator NELSON. If he is just writing a prescription, the package insert is in the drugstore?

Dr. LEE. That is correct.

To return again to my statement, Mr. Chairman, we must begin with the medical schools. Pharmacology, it seems, is the stepchild of medical education. It is both a clinical and a laboratory science. But historically, it has been placed in the preclinical curriculum, far removed from the actual therapeutic situation. The clinical aspects of drug therapy appear to receive scant and insufficient attention and, as a consequence, many students emerge without the thoughtful and critical attitudes that are necessary to make wise therapeutic judgments.

Some forward-looking schools have added a second course in pharmacology, taught during the latter part of the curriculum, in which

stress is placed not only on the use of drugs in actual therapeutic situations but also on the evaluation of drug promotional claims. The task force believes that a clinically oriented course in drug therapy should be made a part of the curriculum in all medical schools, and it has recommended Federal support for this purpose.

We have also been concerned, Mr. Chairman, about the kinds of drug information and continuing education opportunities available to prescribing physicians.

A small number of publications and periodicals do contain the comparative, objective data that are needed. But the existence of these publications, which are highly regarded by expert clinicians, are largely ignored or unknown to the majority of practicing physicians.

Likewise, a small number of medical schools and other health organizations provide regular opportunities through postgraduate courses for prescribers to renew and expand their store of drug information. But these opportunities are relatively scarce and they, too, fail to reach the majority of physicians.

Most of the drug information received by practicing physicians comes from the advertising and promotional activities of drug companies—from printed and graphic advertisements and from drug salesmen known as detail men.

Senator NELSON. Your task force concludes that most of the drug information received by practicing physicians comes from advertising and promotional activities of drug companies and is printed in graphic advertisements and from drug salesmen known as detail men?

Dr. LEE. Yes, sir.

Senator NELSON. That is a fine commentary on the source of information that the great, distinguished medical profession uses in prescribing drugs for its patients. I think it raises a very serious question, and one which it seems to me the American Medical Association ought to be addressing itself to. In all the hearings I have had thus far they seem to be standing on the sidelines unconcerned about the continuing education of the medical profession. That is a disturbing matter to me.

Dr. LEE. We share your grave concern about this, Mr. Chairman. We think this is one of the more important observations made by the task force out of this wealth of material that was accumulated and evaluated. I think it is a matter of grave concern to the profession; it is a matter of grave concern to the medical schools that have the responsibility for providing the basic education for physicians; and, it is of concern to the public. The public should be aware of the fact that their doctors are obtaining their information about the drugs which they prescribe from the advertising provided by drug companies.

From the testimony presented before the subcommittee and from independent studies conducted by the task force staff, it is apparent that drug advertising is steadily being improved by the control of false or misleading claims, and those unsupported by adequate scientific data. Through the enforcement of new FDA regulations and cooperation of leaders in the drug industry, drug advertising is becoming more factual, informative, and accurate than ever before.

Senator NELSON. It is true, however, cases continually appear before the FDA in which the company is making claims for drugs which are not approved by the FDA, is it not?

Dr. LEE. That is correct.

Senator NELSON. We had that testimony last week on precisely that question. So you haven't solved the problem of getting the companies to comply with FDA standards, approved standards and guidelines in advertising of products either in the promotional advertising or in the promotion done by the detail man himself; is that not correct?

Dr. LEE. That is correct. And, of course, this is true not only for the drugs introduced between 1938 and 1962, which are currently under review by the National Academy of Sciences, but also in the drugs more recently introduced. In some of your recent hearings you focused on those problems very specifically.

It concerns me that many, if not most, physicians rely primarily on the companies' promotional material and on the detail men for drug information. The prime function of advertising is to sell drugs, and therefore, one cannot and should not expect such advertising to be fully objective.

Senator NELSON. Let me say at this point, Doctor, it seems to me that one of the serious problems is that the medical profession has had a misplaced confidence in the integrity of the manufacturers of the drugs. And if the manufacturers of the drugs were honestly presenting the case in an objective fashion, the medical profession would be justified in relying upon them.

But when they spend \$600 million a year and develop over a period of years the confidence of the profession, the profession has then been led to believe that they can believe what the manufacturers say. And I think that is the tragedy here. And one of the sad parts of that is that the one group that has the qualifications to intervene and notify the physician that the manufacturers have been overdrawing their claims and making misleading claims is the profession itself, the American Medical Association.

I don't blame a physician if he has great confidence in the integrity of the company and then accepts the claims they make for it. The problem is, his confidence is misplaced and he does not know it. And the FDA has been unable to get through to make clear, apparently, to the profession, and the American Medical Association, their own professional organization has been grossly derelict in their responsibility toward notifying the profession about the improper claims being made by the manufacturers even in their own advertising, in my judgment. It is not wholly the fault of the physician in the sense that he has a misplaced confidence in a great and distinguished American industry.

Dr. LEE. I want to cite a few examples, Mr. Chairman, of some of our concerns. For example, with respect to the selling of drugs and the objectivity of advertising:

That a drug is merely the minor molecular modification of an existing, well-proven product is seldom made known in advertising.

Relative costs are seldom discussed in advertising.

The relative advantages of other drugs in the same therapeutic class are likewise seldom mentioned in advertising.

The task force is concerned not merely with the content of drug promotion, but also its volume. Currently, the drug industry is spending nearly \$500 million per year on drug research and an estimated \$600 million on drug advertising, drug detailing, and other forms of

promotion. The sheer amount of this material has reached supersaturation proportions, and contributes, I am certain, to increasing confusion among doctors.

The task force has made three recommendations which, if implemented, Mr. Chairman, would help restore some balance to the provision of drug information.

First, we reaffirmed our earlier proposal, and yours, for the establishment of a Federal drug compendium, which would list and accurately describe not only the most popular drug products, but all of them, and which would also provide prescribers with some indication of relative costs.

Senator NELSON. Dr. Lee, as you know, I have introduced a compendium bill. The PMA did some kind of a survey which brought out the fact that the majority of the physicians were negative to the idea of a need for a compendium. I assume that is because the majority of them are confident that they are getting accurate, objective information from the drug company, which they are not. If they were, a compendium might not be necessary, although I think there are some other points in favor of such a publication.

You have to be able to compare the products, one product versus another, and one dosage form, and so forth. What about the question raised that it would be such a massive document that it would be unmanageable?

Dr. LEE. We don't agree with that at all. We think it is a perfectly manageable document, and not only that, but it is essential to achieving the objective of having available in the physician's office adequate information about all drugs. The complaints about the size of the volume are misplaced and not correct in our view.

Senator NELSON. Some suggestion has been made by those who oppose a compendium of all drugs that there be a compendium of the 600 most widely prescribed, which according to them, would cover 90 percent of the drugs.

Wouldn't it be correct, if you are talking about massive volume size, that you might very well divide your compendium into two parts: One, a compendium of the 600 more widely used drugs, and put it in one volume, covering 90 percent of the drugs; and in volume II of the compendium, put the balance. Would that be feasible?

Dr. LEE. Mr. Chairman, we don't think that is at all necessary. We don't think it would be a massive tome the size of a complete Webster's Dictionary. Part of the problem is the way in which the information is made available in the compendium.

I might just ask Dr. Silverman to say a word about this, because he has looked into this matter very carefully for the task force.

Dr. SILVERMAN. I think, Mr. Chairman, that producing a compendium consisting of a limited number of drugs based on current frequency with which they are prescribed would bring up this situation. If you so limit this to the 600 or 400, or whatever number you like, sir, most widely prescribed drugs, this—possibly, by coincidence—would omit most of the generic-name drugs on the market.

Dr. LEE. It would put them at a significant disadvantage.

Senator NELSON. I don't exactly follow that. I assume when they say "widely prescribed drugs" they meant prednisone, not Meticorten, Paracort, or other trade name.

Dr. SILVERMAN. Specifically, the low-cost generic-named drug is not in fact widely prescribed.

Senator NELSON. I wasn't thinking of it in those terms. I hadn't thought they were. I thought if you were going to list the drug, prednisone, you would list prednisone and you would list all those who produced prednisone whether it is generic or brand name, not just the company that is selling most of it.

Dr. LEE. That would be the approach that we think would be essential for the compendium. And, of course, really the crux of the resistance to the compendium is that it would be based on the generic name and not on the brand name of the product. The compendium would list drugs primarily by generic name, but also would list manufacturers and the trade name of the product. The organization of the volume would be on the generic rather than on the trade name.

Senator NELSON. I had assumed that there wasn't any dispute about that. Maybe I was in error. Obviously, in the case one was examining in some detail here, prednisone, the range, according to the Medical Letter, 59 cents to \$17.90 a hundred, and their panels of physicians and consultants on the chemical evaluation of the drugs reached the conclusion that they are all equivalents.

So, if you only listed the brand which sold the most, you would be listing Meticorten and you wouldn't be listing Merck or Lannett or American Pharmacal that were running at prices of 80 cents, a dollar, \$2.20. But I have been amazed at the number of doctors I have talked to, when I discussed the price in the article in the Medical Letter, who had been prescribing Meticorten for patients that it was in the marketplace not at \$17.90 a hundred but in the marketplace at 59 cents a hundred. And they have no way of getting the information.

So if you had a compendium, you would know that these others are available in the market.

Dr. LEE. It is essential that adequate price information be available. In most cases this would be relative price information. This is part of the effort to provide physicians with accurate and adequate information.

Senator NELSON. And you are satisfied that you could list them all in the compendium, and obviously supply adequate, objective, detailed, scientific information about the drug?

Dr. LEE. Absolutely; yes.

Senator NELSON. How many drugs would that involve in the compendium?

Dr. LEE. How many drugs would be in the compendium?

Senator NELSON. I don't mean how many brands or generic names, I mean how many different compounds?

Dr. SILVERMAN. About 1,200 distinct drug entities, but the number of products would be perhaps in the tens of thousands.

Dr. LEE. Because of the different companies.

Mr. GORDON. Dr. Lee, you have talked about the most widely prescribed drugs. Are these necessarily the most useful drugs?

Dr. LEE. That is a very difficult question, because you have to consider that in relation to the individual patient receiving a drug prescribed by the individual physician. It is difficult to make a generalization. They were obviously prescribed by individual doctors because they were thought in circumstances and for the particular patient to be valuable for that particular situation or condition.

Based on our evaluation of the most commonly prescribed drugs, the fact that many are available generically, and yet they are prescribed by their brand name, we believe that the cost to the patient is higher than it need be. The cost of drugs is an important area of concern. But to say that they weren't the best drugs for the particular patient is impossible to say. It is very hard to generalize, Mr. Gordon, on that kind of question.

Mr. GORDON. Yet in discussing the role of the physician, you talk about rational prescribing. I question the rationality—

Dr. LEE. The task force also questioned it. Under existing conditions it is difficult, if not virtually impossible, considering the range of patients and the range of medical conditions that the physician has to deal with, and considering the lack of the kind of information that he needs, for the physician to make what we would consider to be rational prescribing decisions. I don't know that this is really possible or is in fact taking place.

Part of rational prescribing includes consideration of price. As you well know, this simply isn't available, or is very difficult to obtain. Most physicians simply don't have it.

Senator NELSON. For instance, you could have what is a very valuable drug, but a drug that was not valuable for the purpose it was prescribed. For example, chloramphenicol is very valuable as a drug, but it is irrationally prescribed when prescribed for acne, hangnails, sore throat, and so forth, as the testimony indicated before the committee. So in that case it certainly isn't a very valuable drug.

Dr. LEE. That is right. All those people for whom it was prescribed who did not have the conditions for which it is almost exclusively needed or for which it is the drug of choice, were the victims of irrational prescribing. You have mentioned a number of conditions for which chloramphenicol is not only not the drug of choice, but is not indicated. In years past it was unfortunately prescribed for a number of other conditions—the common cold, virus upper respiratory infection. In those cases, it was not rational prescribing.

Having been in practice, I know it can be very difficult prescribing correctly for a patient. The decisions are often very difficult, weighing the benefit of a particular drug in a particular patient with the possible side effects of that drug. Then you must add to these considerations the price of the drugs. You have to consider that as one of the elements in rational prescribing.

Second, in terms of the recommendations, we have proposed that the Federal Government either publish or support publication of a journal which would provide up-to-date guidelines on drug therapy. Although the Government might provide the funds, the actual content would represent the independent judgments of experts in drug therapy.

Third, we have urged Federal support for the efforts of local medical societies, medical schools, hospitals, and foundations to provide

continuing education courses for practicing physicians, emphasizing current applications of drug therapy.

Finally, Mr. Chairman, there is the subject of generic equivalence, which has been considered at great length by your subcommittee.

Here it is important to define a few terms. We have used the term "chemical equivalents" to indicate those multiple-source drugs which contain essentially identical amounts of the same active ingredient, in the same dosage form, and which meet all official standards.

Biological equivalents are those chemical equivalents which, when administered in the same amounts, will provide essentially the same biological availability, as measured by such parameters as blood levels or urinary excretion.

Finally, clinical equivalents are those which, when administered in the same amounts, will produce the same therapeutic effect as measured by control of a symptom or a disease.

Using these terms, I believe we can define the central issue quite simply:

Given two drug products which are chemically equivalent, will they give essentially the same clinical effects in human beings?

The task force has given serious study to this matter. In reaching our conclusions, we have reviewed the existing literature. We have had access to the results of new biological availability studies conducted as part of our operations by the Food and Drug Administration, and by Public Health Service hospitals. We have had the advice of workshop participants from the clinics and research laboratories of hospitals, universities, and industry. We have had the counsel of an advisory group on clinical trials, composed of distinguished experts representing clinical medicine, pharmacology, and biostatistics, as well as representatives of the official compendia with their responsibility for the maintenance of drug standards.

We have reached the conclusion that—except in rare instances—drugs which are chemically equivalent, and which meet all official standards, can be expected to produce essentially the same biological or clinical effects.

There are, as I have just mentioned, a few instances on record in which this has not been the case. One of these concerns chloramphenicol, and in this case the nonequivalent products have been promptly removed from the market.

Senator NELSON. All the chloramphenicols were batch tested prior to marketing, correct?

Dr. LEE. Yes, sir.

Senator NELSON. So there was not a USP standard established for that drug, was there?

Mr. GOODRICH. There was a standard established for it. The standard was found to be inadequate in assuring the biological availability.

Senator NELSON. Now, have certain changes in the standard been made?

Mr. GOODRICH. Additional proof of biological availability, using human volunteers, has been required as a prerequisite to certification. In addition to the chemical standard, we have found that it is necessary to test the formulation to make sure it gives a reliable blood level response.

Senator NELSON. Does this happen to be one of those rare drugs where the only test of equivalency is in fact a clinical test, or a biologic test, at least?

Dr. LEE. That is correct. In the case of chloramphenicol we have found that a biological test is required. We believe, however, that it is not necessary to have an additional clinical test in the treatment of disease when equivalent blood levels have been produced.

Senator NELSON. What I am getting at is whether the companies have now been admitted back to the market?

Mr. GOODRICH. By presenting evidence showing an adequate blood level response to the formulations. Now, this is not a situation such as we had some years ago with intrinsic factor in which you required a biological test for each batch. To the contrary, this is a formulation examination, some sharpening of the chemical standards, and on top of that, a requirement of the study of biological availability to make sure the drug was getting into a proper blood-level situation.

Senator NELSON. But those chloramphenicols were removed from the market and in order to come back on the market, they had to present a test of biological equivalency, and they have done that?

Mr. GOODRICH. Yes, sir.

Senator NELSON. Have you been able to establish an objective test out of all this? What have the firms done to their production methods that made the drug more quickly available physiologically, and if they have done something specific, could that be put into the standard?

Mr. GOODRICH. We should have our scientific people answer that in detail. I would be afraid to try to give you the exact details. I do know that some formulation changes were made, and that the tests of biological availability were required.

Dr. LEE. I think it is important also, Senator Nelson, to add that the FDA also requires good manufacturing practices and quality controls, so that we can assure the public that the steady flow of the drugs into the marketplace continues to meet the standards. To assure compliance the FDA carries out plant inspection and also test drugs obtained in the marketplace.

It isn't just meeting the standard. If we didn't have these other factors built in through the Food and Drug Administration I think it would be difficult to give the kind of assurance that is necessary.

Senator NELSON. Doctor, I will have to leave for 10 minutes. The Interior Committee has some important measures to dispose of, and they need me to constitute a quorum. So we will recess for 10 minutes, and I will be back.

(Recess.)

Senator NELSON. Please go ahead, Doctor.

Dr. LEE. Mr. Chairman, before returning to my statement, in your absence I reflected a little bit on the question that you and Mr. Gordon raised earlier with respect to the compendium. There is a point that requires more clarification. This has to do with the most commonly prescribed drugs and why we shouldn't list and describe them in a single volume and then list and describe the rest of the drugs in a second volume. The assumption behind this proposal is that this first volume would be the most frequently used by the physicians, and would be less bulky and more easily used.

Based on our studies and our conclusions regarding rationality and irrationality of prescribing, it could well be that if we put 400 or 600 drugs in this volume I, that we would be including a large number of drugs that were being prescribed not in a rational fashion. At the same time we might be describing the best drugs, the most appropriate drugs in the other, little used volume. This was a point that I really didn't make clear in my earlier statement as to why we believe that all drugs should be listed generically and not in relation to frequency of use. I think it was implicit in what you were saying and it is a point that needs to be emphasized.

Senator NELSON. On the problem of volume size, I guess in any event you could resolve it if it were too bulky, you could still have two or three volumes.

Dr. LEE. Surely you could, but it shouldn't be on the basis of frequency of prescribing.

Senator NELSON. Yes.

Dr. LEE. There was one other point while we are on this subject. In discussing the guidelines for physicians on drug therapy, I would just like to make a little clarifying point on that. One of the examples in the United States of such material is the Medical Letter. In Great Britain the Government publishes a Prescribers Journal.

I don't know if you have seen this. But it is a Government publication. The authors of these articles are totally independent of the Government. The journal includes excellent summary information on drugs for particular disease conditions. It is the sort of thing that I had in mind in my testimony, but in going over it quickly I did not emphasize this point.

Senator NELSON. This publication, as I understand it, is circulated in Great Britain, New Zealand, and Australia; did you say that in your testimony?

Dr. LEE. No; I didn't say that in the testimony. That is why I wanted to make the point. It is in the report, but it is not in my statement.

Senator NELSON. I saw it in the report.

Dr. LEE. That is right.

Senator NELSON. Has this publication received some public funds for support?

Dr. LEE. This is a Government publication.

Senator NELSON. It is a Government publication?

Dr. LEE. Yes, sir. It goes to the physicians without charge. In this country, a physician can subscribe to Medical Letter, but the number is rather small, perhaps 10,000 to 20,000 physicians.

Senator NELSON. We had testimony on that. I thought it was 10 out of some 200,000.

Dr. LEE. Yes.

Senator NELSON. Is this also in the nature of a compendium?

Dr. LEE. No. The Medical Letter and Prescribers Journal are quite different. They are what I call a guide to rational prescribing.

Senator NELSON. This is just a continuous flow of current information to the physicians; is that right?

Dr. LEE. Correct; by people who are expert in their particular field. It is very useful, but it is not readily available in this country.

On the question of drug prices, Dr. Novitch has brought to my attention a very simple chart which the Ministry of Health makes available periodically to the physicians.

Senator NELSON. We will put that in the record at this stage in your testimony.

(The document referred to follows:)



Comparative Costs of
ANTIPYRETICS AND ANALGESICS

NOTE This list of preparations has been compiled from those commonly prescribed on Form E.C.10. The cost includes professional fee etc. The actual cost of treatment will, of course, depend on the dosage used.

Preparation	Total N.H.S. Cost of 25 Tablets/Capsules			
	2/-	4/-	6/-	8/-
Aspirin Tablets, B.P. 5 gr.				2/7
Aspirin Soluble Tablets, B.P.				2/10
Codeine Compound Tablets, B.P.				3/1
Paracetamol Tablets, B.P.				3/1
Solprin Tablets				3/1
Codeine Compound Soluble Tablets, B.P.				3/5
Codis Tablets				3/10
Hypon Tablets				3/10
Veganin Tablets				3/10
Panadol Tablets				3/11
Myolgin Tablets				4/2
Paynocol Tablets				4/5
Panasorb Tablets				4/8
Codeine Phosphate Tablets, B.P.				5/1
Distalgesic Tablets				5/4
Palaprin Forte Tablets				6/1
Panadeine Compound Tablets				6/1
Norgesic Tablets				6/6
Zactirin Tablets				6/6
Ponstan Capsules				6/7
Zactipar Tablets				6/11
D.F.118 Tablets				7/-
Rinurel Tablets				7/5
Equagesic Tablets				8/-

Issued by the Ministry of Health
(E.C.L.43/66)

October, 1966
D76109/1/551v 75m 10/66 CL

Dr. LEE. It is just a simple, graphic statement, and very helpful to the physician. It is just a reminder. That could be issued in addition to the periodic updating of the compendium, which would include the information on prices. This sort of thing could be issued monthly or more often than that, if necessary.

Senator NELSON. I don't quite understand the graph at the first glance at it. Can you explain it?

Dr. NOVITCH. Mr. Chairman, this chart, published, I believed, in 1967, compares the prices of various analgesics and antipyretics—drugs for pain and fever. At the top is simple aspirin. It shows the cost of 25 tablets to National Health Service to be about 30 cents in U.S. currency.

Others are listed in the ascending order of cost. At the bottom, the most expensive is a combination product containing aspirin and meprobamate. And it sells for about 96 cents in U.S. currency. Others are single active agents selling for almost the maximum price listed.

The impression which the Ministry seeks to convey to practitioners is that—this comes along with the Prescribers Journal—some of the standard preparations are quite effective and available at less cost than some of the more expensive products on the market.

Senator NELSON. Thank you.

Dr. LEE. Is it a matter of communicating really relative costs in a very simple direct fashion, and I think quite an effective fashion.

To return to my statement—

Mr. GORDON. May I ask a question, Dr. Lee?

Since that seems to be a rather simple type of publication, and it probably wouldn't be too expensive to publish it, why can't the Department of HEW publish it under its existing authority? Specifically, I have in mind section 705 of United States Code 21, where the Secretary may cause to be disseminated information regarding food, drugs, devices, and so on and so forth, dealing with the health and welfare of the people.

Dr. LEE. Several things. One is, I think that such a publication by a Government agency might be less acceptable to the medical profession than a non-Government publication even though the same people wrote the articles.

Second, if we were to undertake such a publication—it is an important part of our recommendation—and if the decision was made to do so, we would certainly want it thoroughly discussed before Congress as to whether it should be a Government or non-Government publication. I think that kind of issue should be thoroughly aired before the Congress because I think you would want to hear the alternatives, the costs of alternatives, and their likely acceptance before a final judgment was made.

Mr. GROSSMAN. Doctor, may I ask you a question with regard to equivalency? Could you tell me how many drugs you tested to date in making a determination?

Dr. LEE. How many drugs we have tested in the Food and Drug Administration and the Public Health hospitals?

Mr. GROSSMAN. Yes.

Dr. LEE. Dr. Novitch.

Dr. NOVITCH. The present Food and Drug Administration tests are concerned mainly with antibiotics. A total of 44 products—that is, representing all manufacturers—are under test now. The exact number of drug entities involved is less than a dozen. Two drugs are under study in Public Health Service hospitals.

Mr. GROSSMAN. Do you anticipate that more drugs will be tested?

Dr. NOVITCH. Yes. We have not only recommended that the tests continue, but that Federal funds be expanded.

Mr. GROSSMAN. Let me ask you this for information. You say you reached the conclusion that except in rare instances drugs which are chemical equivalent, et cetera. Is this conclusion based on what you have done in the past, or what you surmise will continue in the future, or how does this work?

Dr. NOVITCH. It is based largely on past experience. But also, the goal of FDA's present efforts is to seek new standards which could make it possible eventually to use laboratory tests in place of the biologic availability studies that are now required with chloramphenicol. The major goal is to achieve some sort of correlation between prospective new standards and the clinical studies that are now underway.

Dr. LEE. Of course, this also involved a review of the available information and the literature on various studies that had been done.

Mr. GROSSMAN. My problem is, you say this is your conclusion, and I assume based on a thorough, complete, final study.

Dr. LEE. As new drugs emerge, new studies will be required. Thus it has to be a continuing study. This has now been established as a continuing activity within the Department.

Mr. GROSSMAN. Am I correct in saying that as far as all drugs that are presently on the market are concerned, you would make this conclusion or statement?

Dr. LEE. Yes, you can draw that conclusion from our statement.

Mr. GROSSMAN. And have all drugs in fact been tested for this purpose?

Dr. LEE. For clinical equivalency, no. But you think that, based on the evidence that we examined, both from the literature and from the clinical studies and from the biological studies, from the standards that have been developed over a number of years, our conclusion was that there are relatively few where there will not be clinical equivalence when you have chemical equivalence.

Senator NELSON. Meeting USP—

Dr. LEE. Meeting the standards. And, of course, we are updating the standards. Efforts are currently underway to update those standards.

Mr. GROSSMAN. Dr. Lee, I think it was in the New York Times of Tuesday, July 16—I remember when this came out, because there was a big furor about it—and since that time I have heard different reports as to what the truth was of the article which appeared, I think, in the Washington Post, implying that the FDA had found that there were differences in drugs in equivalency.

I know it mentions chloramphenicol specifically, but it also mentioned other drugs. There was a lot of confusion, and I heard this was a false report, and somebody let this out when it shouldn't have come out. Can you clear this up for us?

Dr. LEE. I am not exactly certain of the study to which you referred, but I believe it was the study that was conducted at Georgetown University. And if I recall correctly—we can provide you a more detailed statement for the record—there were three drugs. One was chloramphenicol, and one was a sulfa drug, and the other was diphenylhydantoin, which is used for the treatment of epilepsy.

In the drugs that were tested the requirements differed. The sulfa drugs, which are used primarily to treat urinary tract infections, required the careful analysis of the urinary excretion rates and the

availability of the drug in the urinary tract on an around-the-clock basis.

In the testing of drugs used for the treatment of seizures, one of the generically equivalent drugs was absorbed more rapidly and had a higher blood level than the brand name drug. In this case it might be necessary to do clinical studies to determine if that is clinically equivalent, clinically effective when you find these biological differences.

There are some statistically significant biological differences that we did not consider clinically important and which Dr. Ley, in commenting on this report, did not consider significant. At the time of the publication of the report the implication was made that you could generalize from the study of these three drugs.

Mr. GROSSMAN. It says, "Already the statistics have shown that two grams of the drug may have the same chemistry and behave differently in the human body." And the whole emphasis of the article is to show that, with a big picture of Dr. Ley setting next to you right here.

Dr. LEE. We can provide you with Dr. Ley's statement made at the time, because I think that clarifies it. It is difficult recalling from memory the content of an article published 2 months ago. But I would be glad to supply more detailed information on those three particular drugs.

Mr. GROSSMAN. I would appreciate that. Thank you.

Mr. GORDON. As I understand it, as far as the sulfa drugs are concerned, the differences were not clinically significant; is that correct?

Dr. LEE. That is my impression; Mr. Gordon. I believe that the differences were not statistically significant. To be certain, however, we will provide that for the record. I don't want to try to recall this from memory when we do have and can provide you with specific information.

(The subsequent supplemental information submitted by Dr. Lee follows:)

In late 1967, Parke Davis and Company presented data to the Food and Drug Administration indicating that several brands of chloramphenicol on the market gave lower blood levels than those produced by the preparation for which the Parke Davis' new drug application had been previously approved. Under its contract with Georgetown University, the FDA arranged for blood level studies on chloramphenicol, and a number of other drugs, including sulfisoxazole, and sodium diphenylhydantoin.

Dr. Christopher M. Martin and associates at Georgetown administered chloramphenicol capsules to healthy volunteers in a group of studies comparing the blood levels of Parke Davis' Chloromycetin with those of two generics. Georgetown concluded that the generic chloramphenicol capsules gave significantly lower blood levels than Chloromycetin and the drugs could not be considered therapeutically equivalent to the Parke Davis product. FDA then conducted further experiments on chloramphenicol capsules from other manufacturers, and its conclusions were similar to those of Georgetown.

Similar experiments, also on healthy volunteers, were conducted at Georgetown with three different manufacturers' sulfisoxazole tablets and three manufacturers' sodium diphenylhydantoin capsules. The FDA's review of these data led to the conclusion that there were no significant clinical differences between the three sulfisoxazole products. The data developed from the diphenylhydantoin experiment, are indefinite, and do not permit a conclusion of any clinical significance with respect to these drugs at this time.

Data from the Georgetown work have been useful to the FDA, but these studies provide no basis for concluding that generic products "work less well" than the brand-name product.

Dr. Christopher Martin later presented a paper on the studies on the three drugs which had been conducted for the FDA at Georgetown University before the American Society for Pharmacology and Experimental Therapeutics at the University of Minnesota. In announcing his results, Dr. Martin implied that all of these drugs showed a lack of equivalency. Since his conclusions were without proper justification, the Commissioner of FDA issued the attached press release on August 20, 1968, setting forth FDA's position with respect to the Georgetown study on clinical equivalency.

[For release, p.m.'s, Tuesday, Aug. 20, 1968]

"The Food and Drug Administration has in no sense concluded that 'generic' drugs are less effective as a class than 'brand-name' products," FDA Commissioner Herbert L. Ley, Jr., M.D., declared today.

"In my opinion, there are fewer than two dozen drugs where therapeutic differences among competing products may be a problem," he said.

Dr. Ley's comments were made in response to a report today on the results of studies on three drugs conducted for the FDA at Georgetown University. Dr. Christopher M. Martin presented the paper at the fall meeting of the American Society for Pharmacology and Experimental Therapeutics at the University of Minnesota.

"Data from the Georgetown work have been useful to the FDA, but it is completely unwarranted to reach any general conclusions about drug equivalency on the basis of these exploratory studies," Dr. Ley said.

Only one of the three drugs tested showed a clinically significant difference in blood levels produced by the various products administered to volunteers, the FDA Commissioner pointed out.

"Jumping beyond that to the conclusion that there are serious doubts generally about the effectiveness of 'generic' versions of drugs simply isn't valid," Dr. Ley said.

The FDA now is sponsoring comparative studies on more than a dozen drugs, but Dr. Ley said the Agency will not announce its conclusions until it has accumulated definitive data.

Senator NELSON. Just on the point of your conclusion that when drugs are chemical equivalent and meet all the chemical standards they are therapeutically equivalent except in rare instances, as you are aware, we have had distinguished pharmacologists and clinicians appear before the committee and give the same testimony. And I assume that when you refer to the fact that you have relied upon the literature, and clinicians, and past experience, and so forth, that that also involves the rather vast experience of the Defense Supply Agency, the VA, and general hospitals and others who buy on competitive bidding. And on one occasion they get one brand of prednisone or one brand of chloramphenicol—that isn't an example—one brand of another drug.

Dr. LEE. Tetracycline.

Senator NELSON. And their experience over the years has been that if they meet the same standard and have the same chemical composition, that they are therapeutically equivalent; is that correct?

Dr. LEE. That is correct. Because this is a highly charged and controversial area, the task force made a very extensive study. The task force study has been going on for well over a year. We consulted with the leading experts in the field; our staff reviewed the literature; we had the special studies carried out; we reviewed the experience of the Defense Supply Agency and other agencies who have had just the kind of experience that you have described. Our conclusions really are based on a detailed examination of the information that is available today.

Senator NELSON. Thank you.

Dr. LEE. To return to my statement, and the comment that Dr. Goddard, former Commissioner of Food and Drug made, he expressed the view that such nonequivalency might be found among perhaps two dozen drugs. Nothing which has been discovered during the past year has caused the task force to dispute Dr. Goddard's prediction.

Nevertheless, Mr. Chairman, it is evident that the issue of chemical equivalency and clinical equivalency has been clouded by articles, publications, press statements, and promotional claims which seem designed to make the issue appear much larger.

One example is a recent publication entitled "Bibliography on Biopharmaceutics," which contains 501 documented references dealing with the influence of pharmaceutical formulation on the therapeutic activity of drugs. According to its publisher, this volume supposedly refutes what is termed the "myth of therapeutic equivalency."

We have had this book reviewed by the professional staff of the task force, by the Food and Drug Administration, and by our consultant experts. They are in agreement on the following points:

1. The publication is a useful compilation of references on the subject of biopharmaceutics.

2. Of the 501 references, only 221 were actually conducted in human subjects.

3. Of the 221, only 76 were—by the authors' own evaluation—adequately designed or controlled experiments.

4. Of the 76, only 12 represented comparisons between what might seem to be different brands of the same chemical equivalents.

5. Of these final 12, most compared different dosage forms—such as tablets versus effervescent solutions—or different salts—such as sodium derivatives versus potassium derivatives or different coatings—such as delayed release products versus rapid release products. Some of the products studied failed to meet existing USP or NF standards, and thus would be illegally on the U.S. market.

And just to make the point, Mr. Chairman, 12 out of 501 references.

Accordingly, it appears that there were only two or three which demonstrated statistically significant lack of clinical equivalency, and in one case, the differences were described as being without any practical clinical importance.

The finding that only two or three of the 501 citations in this book represent significant lack of clinical equivalency would therefore seem to be consistent with the statement in the task force report that "lack of clinical equivalency among chemical equivalents meeting all official standards has been grossly exaggerated as a major hazard to the public health."

Senator NELSON. I might say that I read the Pharmaceutical Manufacturers Association release on this, and I was quite astonished. And then I wrote to the Secretary of HEW, Mr. Cohen, and called this to his attention, and then received a memorandum analysis back from Dr. Silverman, who analyzed this.

I think this is one of the problems—I think this is just another example of the association itself again making a terribly misleading claim which just doesn't hold water at all—and this has happened time after time after time—a distorted picture which may stand now totally refuted by the analysis of the Department of Health, Education, and Welfare.

And I am just curious to know when the Pharmaceutical Manufacturers Association is going to stop this nonsense, and, as Mr. Stevenson said one time, talk some sense to the American people. It gets a little worrisome spending time checking on the accuracy of PMA's statements. But this kind of statement gets circulated widely over the country, and the doctors read it, and the doctors say, it is true again, there is no generic equivalency, we have got another piece of proof. And probably by the expenditure of millions and millions of dollars they just brainwash the country with falsehoods.

And every time I catch them we are going to have a public hearing and expose them. If nobody else is going to do it, I am going to do it, because they are doing a disservice to the public health and the medical profession, and they are doing a disservice to the drug companies they represent, and they ought to be pulled up short on the halter when they do it.

And I am pleased to have this documentary evidence placed in the record. And I will insert the letter of Mr. Cohen as well as the response of Dr. Silverman.

(The information referred to follow :)

SEPTEMBER 9, 1968.

HON. WILBUR COHEN,
Secretary, Health, Education, and Welfare,
Washington, D.C.

DEAR MR. SECRETARY: On August 5, 1968 the Pharmaceutical Manufacturers Association distributed a "Bibliography on Biopharmaceutics" accompanied by a press release, both of which are attached.¹

Since your Department's Task Force on Prescription Drugs has been concerned with the matter of therapeutic equivalency, I would appreciate your comments on the attached documents.

Kindest personal regards,
Sincerely,

GAYLORD NELSON,
Chairman, Subcommittee on Monopoly.

NEWS RELEASE OF THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION

WASHINGTON, D.C., August 5, 1968.—The scope and importance of the science of "biopharmaceutics" are detailed in an extensive bibliography just published by the Pharmaceutical Manufacturers Association.

"This unique publication refutes the astonishing myth that there are no significant differences among dosage forms of the same drug," C. Joseph Stetler, president of the association, said.

The bibliography contains abstracts and journal references on the influence of pharmaceutical formulation on the therapeutic activity of drugs. Listed are 501 citations. They establish a literature base in a field where, in a broad sense, some ten thousand articles are published annually.

The compilation is an outgrowth of testimony presented before the Monopoly Subcommittee of the Senate Small Business Committee. In these hearings some witnesses suggested that differences in formulation of drug products were negligible or of minor significance in their effect on patients.

"The bibliography lists well-designed clinical studies to show the opposite is true," Mr. Stetler said. "They describe clinically measurable differences among widely varying and widely used classes of drugs beyond those already documented in the hearings."

"Since different formulations of the same drug made by the same manufacturer may produce different results in patients, it is hardly surprising that the same drug made by more than one company may differ even more markedly," Mr. Stetler explained. "No two companies make a drug in exactly the same way."

¹ The "Bibliography on Biopharmaceutics" has been retained in committee files.

Thus the variations denoted in the articles of this bibliography, whether subtle or pronounced, can have significant effects in patients."

"It is interesting to note," the PMA executive added, "that the extensive research required for this study failed to turn up a single reference establishing that all formulations of the same drug from a variety of sources are equivalent—or even probably equivalent. Yet this invalid assumption has been made repeatedly in proposed legislation at both state and federal levels."

Studies in the compilation indicate that drug uniformity cannot be established simply by testing the end product.

"Thus compliance with such standards as the United States Pharmacopoeia and the National Formulary is no guarantee of product effectiveness in actual patients," Mr. Stetler asserted. "This is not to imply any criticism of the USP and the NF, both of which have done outstanding work in developing drug standards. But it is to say that therapeutic equivalence can only be shown in the clinic or by well-designed *in vivo* or *in vitro* presumptive testing, complex and exceedingly costly as this may be."

"In the final analysis, the excellence of a product must depend upon the excellence of the manufacturer. There are no substitutes for quality control of a high order and consistently good manufacturing practices," Mr. Stetler said.

The PMA president pointed out that because of budget and manpower the FDA concentrates its inspections in major company plants, being unable to give much attention to the smaller firms that have the greatest number of product recalls.

"Yet member firms of the PMA, producing 95 percent of the nation's prescription drug supply, have only 20 percent of the recalls. Companies making only five percent of available drugs are identified with 80 percent of the recalls despite little regulatory attention. Such a record should be a warning to those who blandly assume the equivalency of drugs produced under a variety of conditions," he stated.

"To deny that formulation is important is to deny the very basis of the profession of pharmacy," Mr. Stetler said.

Of the 501 citations in the bibliography, 221 cover *in vivo* human studies, with the remainder concerned with studies in animals as well as *in vitro*. About 20 percent appeared originally in the *Journal of Pharmaceutical Sciences* of the American Pharmaceutical Association.

"It should be borne in mind," the preface to the bibliography states, "that there is a massive body of information concerned with such subjects as: the stability of an active ingredient in a pharmaceutical formulation and the stability of the formulation itself as well as with preservatives, sterility, flavors, and other significant pharmaceutical factors which ultimately affect the therapeutic activity of a drug. Articles on these topics, however, were generally excluded..."

(Definition of biopharmaceutics: a field encompassing the study of the relations between the nature and intensity of the biological effects observed in animals and man and the following factors—the nature of the form of a drug, such as ester or salt; the physical state, particle size and surface area; the presence or absence of adjuvants; the type of dosage form; and the pharmaceutical process used in manufacturing).

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., September 24, 1968.

HON. GAYLORD NELSON,
Chairman, Subcommittee on Monopoly, Select Committee on Small Business,
U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: I have asked the professional staff of the Department's Task Force on Prescription Drugs to review the Pharmaceutical Manufacturers Association publication, *Bibliography on Biopharmaceutics*, as requested in your letter of September 9.

I am enclosing for your information a report prepared by the Task Force staff director, Dr. Milton Silverman.

Sincerely,

WILBUR COHEN, Secretary.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
OFFICE OF THE SECRETARY,

September 13, 1968.

To: Philip R. Lee, M.D.

From: Milton Silverman, Ph. D.

Subject: Bibliography on Biopharmaceutics.

On August 5, 1968, the Pharmaceutical Manufacturers Association released a publication entitled *Bibliography on Biopharmaceutics*, citing 501 references on the influence of pharmaceutical formulation upon the therapeutic activity of drugs.

In an accompanying news release, a PMA spokesman stated: "This unique publication refutes the astonishing myth that there are not significant differences among dosage forms of the same drug."

This statement in itself is somewhat astonishing. Among responsible scientists and clinicians, we are not aware of any doubt that there may be significant differences. The important question is how often these differences occur, and what threat they pose to the welfare of patients.

Here it is important to agree on the groundrules for the analysis—obviously, there will usually be substantial clinical differences between two products in different dosage forms, such as one in solution and one in tablets, or one in a coated tablet and one in an uncoated tablet.

But that is not the issue. The important question is whether or not there will be clinically important differences when two different products, containing essentially the same amounts of the identical active ingredients, in the same dosage form, both meeting USP, NF or other official standards, are administered in the same way—and whether this can be demonstrated in human subjects through properly designed, valid experiments.

With this in mind, it seemed desirable for the Task Force, its consultants, and the Food and Drug Administration, to review the new publication, with its 501 references. The following points were obvious:

Of the 501 references, only 221 were actually conducted in human subjects.

Of the 221, only 76 were—by PMA's own evaluation—"adequately designed or controlled" experiments.

Of these 76, only 12 represented comparisons between what might seem to be different brands of the same chemical equivalents.

And of these final 12, most compared different dosage forms (such as tablets versus effervescent solutions), or different salts (such as sodium derivatives versus potassium derivatives), or different coatings (such as delayed release products versus rapid release products). Some of these final products failed to meet existing USP or NF standards, and thus would be illegally on the U.S. market.

At the most, Task Force staff and our consultants agree, there were only two or three which demonstrated statistically-significant lack of biological equivalency, and in one case, the differences were described as being without any practical clinical importance.

In summary, it seems evident that the new publication represents a useful compilation of the literature on this subject.

The finding that only two or three of the 501 citations in this book indicate significant lack of clinical equivalency would seem to be consistent with the Task Force statement that "lack of clinical equivalency among chemical equivalents meeting all official standards has been grossly exaggerated as a major hazard to the public health."

Dr. LEE. Mr. Chairman, I have tried to suggest several of the major issues pertaining to the use of prescription drugs which both your subcommittee and the Secretary's task force have examined in very considerable detail. As you know, the work of the task force—like that of the subcommittee—has been much more extensive than is reflected in my presentation. And our work is continuing, leading, as I have indicated, toward recommendations on the vitally important—indeed central—question of including under medicare coverage of the cost of out-of-hospital prescription drug costs. This

issue alone is of tremendous importance to the task force, your subcommittee, and the American people.

My colleagues and I will be pleased to answer any questions you may have.

Senator NELSON. I would like at this moment to just read into the record a paragraph from a letter I received from Dr. Robert E. Howard, of Cincinnati, Ohio, president of Ohio State Medical Association, a letter dated October 18, 1967.¹ The reason I read this paragraph is because it is, I think, a rather dramatic example of how successfully the manufacturers with their advertising have brainwashed distinguished medical people in this country. Listen to what he says in the paragraph:

We have not even produced any scientific data or substantive expert testimony which has been offered the subcommittee to support the claim of generic equivalence of drugs. Indeed, we are certain that such evidence has not been placed before you because we know it does not exist.

I don't know how he knows it does not exist but he knows it somehow.

A comprehensive study of this question, so basic to your entire inquiry, is now being made with the Department of Health, Education, and Welfare at the direction of the President. When it is completed, we feel confident it will illuminate the fallacy of so-called "generic equivalent." We urge you to withhold until then judgment on the testimony, the sweeping claims, the unsupported generalizations you have heard over the past several months, for without incontrovertible scientific evidence, this controversy cannot be resolved by the public or the Members of Congress.

Dr. LEE. I would just comment, Mr. Chairman, that we believe now that we have made that scientific evidence available to the committee. Certainly we have reviewed it, and it forms the basis of our recommendations.

Senator NELSON. I just want to commend the HEW for what I think is an exceptionally fine start on the evaluation of a rather comprehensive problem, and I think it is a great public service.

Dr. LEE. We hope that the background documents, Mr. Chairman, which we will be making available, and of which initial publication is to start fairly soon, will be very useful far beyond their value to our task force. We believe they will be very useful to your subcommittee, and to many other committees of the Congress, to the scientific community, to physicians, and to consumer groups for further analysis and evaluation. There is really a wealth of material available in these background documents, and we think that it will add to public understanding of the problem, as well as a better understanding by the scientific community and the medical profession of these complex problems.

Senator NELSON. As these various task force reports become available, it will probably be valuable and helpful if we could have hearings on them and explore the implications of what your findings are for our own hearing record, if you are willing to appear on them.

Dr. LEE. We would be delighted to do so.

Senator NELSON. Mr. Gordon.

Mr. GORDON. Dr. Lee, in the release issued by the Pharmaceutical Manufacturers Association is the following statement: "In these hearings"—referring to the hearings held by this subcommittee—"some

¹ See app. I, p. 3861, *infra*.

witnesses suggest that differences in formulation of drug products were negligible or of minor significance in the effect on patients."

As far as I know, none of the witnesses before our subcommittee discussed differences in formulation of drug products. The subject we discussed was clinical equivalency. Would you explain for the record the difference in the meaning of these two terms?

Dr. LEE. The formulation of drug products—there are a variety of factors that go into that in their different dosage forms. A single drug may be prepared as a capsule, tablet or in liquid form. There are also different kinds of liquid preparations. These are different dosage forms. In the formulation of a tablet changes can also be made, for example, different degrees of compression of a tablet may produce different effects biologically or clinically.

There are a number of factors that go into formulation. In certain cases the different formulations will affect either the biologic equivalence or the clinical equivalence of a particular chemically equivalent drug. But what we are talking about when we are talking about clinical equivalence or biological equivalence, we are talking about the identical dosage forms, and we are not talking about different formulations. I think that should be made clear.

Mr. GORDON. This really tends to confuse rather than illuminate.

Dr. LEE. I would agree with your statement.

Mr. GORDON. Doctor, on page 61 of your task force report you say that one of the prerequisites for rational prescribing is knowledge by the physician of "the advantages or disadvantages of alternative forms of therapy."

As I understand it, the physician must know the relative safety and efficacy of drugs to determine which one is most suitable for his patients. Am I correct in that?

Dr. LEE. Yes.

Mr. GORDON. How can the average practicing physician make such determination, even if he had the labeling?

Dr. LEE. He bases it, of course, on various sources of information that he has. His interpretation of this information, and the particular circumstance under which he is prescribing the drug for an individual patient.

We don't have, as I indicated, in a form readily available to physicians the kind of information that is available to the British physicians through the simple, regular Prescribers Journal furnished by the Government. The Medical Letter fills that need for those physicians who utilize it. It is an excellent publication. But unfortunately most physicians don't receive it and don't read it. As a result there isn't available to most physicians an up-to-date comparative evaluations of drugs with respect to given conditions.

There are a number of textbooks that have been published and are available to physicians, but I am sure that they are not in every physician's office. Usually, when faced with a question about a drug, the physician will turn to a book that consists of paid advertising, the Physicians' Desk Reference. The material in there, of course, includes information on post-1962 drugs, and it also included information on drugs from 1938 to 1962, and even before. Because it may include data on these earlier drugs we can't always have assurance that that includes the best information available on effectiveness.

There is not included in PDR the kind of objective comparison that I think would be most beneficial to the physician. Even the specialist physician—that is, one who deals with people with a limited number of conditions, let's say a rheumatologist—for considerable difficulty in making judgments as to one drug versus another in an individual case. It is a tough proposition, even if you are well informed about a narrow area, to keep up to date. It is difficult to make the judgments, I would say, under the best of circumstances.

Mr. GORDON. Do you think that the compendium will eventually carry this type of information?

Dr. LEE. No, that is not the intention of the compendium. I think we need, as I indicated in my testimony, information to the physicians on an up-to-date basis on the alternatives. Again, I cite the Medical Letter and the Prescribers Journal which is available to British physicians, that is the kind of information the physician needs on a regular basis. These prescribing guides, if you wish to call them that, are quite different from the proposed compendium, which would be a compendium of all the drugs. The compendium would be a reference for the physicians, and would include price information.

I see those as two different, but complementary, sources of information that are essential for the physician today as drugs get more potent and as problems get more complex. Just as the potential for good is much greater, the potential for harm is very much greater because of these advances in drug therapy. In the reference I cited in my testimony, of a group of patients in a chronic disease hospital, 35 percent of them had adverse reactions of one sort or another to drugs which had been prescribed by physicians in an institutional setting where they were obviously very concerned about the problem.

Senator NELSON. In your testimony you state that the promotional activities of the drug manufacturer to advertising displays and detail men were, in the judgment of the task force, the most influential factor on the prescribing habits of the physician.

Last week we had 3 days of hearings, and three cases were presented by the FDA showing three different drug firms that had gone beyond the approved and agreed limits in making claims for their drugs, especially the detail men. Do you have any ideas—since this is such an important factor in the prescribing practices of the physician—do you have any ideas on how we could better control this activity, particularly by the detail men?

Dr. LEE. Of course, you put your finger on an area that we are just beginning to really look into in great detail. The Food and Drug Administration has, since the 1962 amendment, taken on certain priority areas, and has dealt with these, I think, with vigor and effectiveness. I would like to ask Mr. Goodrich to say just a little bit about the present efforts to understand more of the activities of the detail men, and to see what in fact can and should be done to deal with the problem, because there is no question about it, it is a problem.

Mr. GOODRICH. Simply as we noted last week, Senator, when we were testifying here, after we received the sales bulletins which you were good enough to send us, it became obvious to us that we needed a good deal more information about detailing practices.

And so we organized an investigation which has been started to get together information both on the printed materials that are used by

detail man in showing—in explaining his product to the prescriber, and the sales material, if we can get ahold of it, that is used within the company in educating the detail man, the bulletins, the training bulletins, and training things of that kind.

This investigation has just started and will be pursued until we get enough information on this important aspect of drug promotion to have some judgments on it. And this is where we are at the moment.

Dr. LEE. We really don't know enough at the moment, Mr. Chairman—and I think that you have really highlighted this area as a singularly important one. It is one where we will be attempting to get the kind of information that is necessary to make wise and sound judgments.

Senator NELSON. You don't have any notion of when that aspect of your task force study will be completed?

Dr. LEE. This is not a task force function, this is a responsibility of the Food and Drug Administration, and it is an ongoing responsibility.

Senator NELSON. And the remaining investigation of this specific point now?

Dr. LEE. Yes, sir.

Senator NELSON. I had just one more question. The minority counsel raised the question about the testing of drugs by the FDA. It occurred to me that you might have been thinking of the program launched by Dr. Goddard to take a certain number of commonly prescribed drugs and work up a comparison of equivalency among the various compounds—the various makes of the same drug. Is that program proceeding now? What is the status of it?

Dr. LEE. Dr. Silverman, do you want to describe the current status?

Dr. SILVERMAN. I think, Senator, that it might clarify the situation if I could throw a few dimensions of this ball game into the testimony.

There has been a good deal of discussion, sir, about the magnitude of this problem, with the possibility that many hundreds or thousands of drugs would have to be tested, and that this would be beyond the present or possibly the future potentialities of the Government. The actual situation is far from this, sir. I think I can illustrate this best by indicating the actual number of drugs that might require testing. We have looked at this very carefully in terms of the drugs which are now used by the elderly. We have studied the top 400-odd, and with very minor exceptions, these would probably apply to the population at large.

Senator NELSON. When you say hundreds, are you talking about 400 different—

Dr. SILVERMAN. Drug entities, which may represent many times this number of products.

Of these, approximately 70 percent or more are still under patent. There are no generic equivalents legally on the market. Of the other 30 percent, a number have chemical or physical characteristics which would make them seem less essential for testing.

Here we have set up our own series of priorities. We have taken those drugs which in the first place are, in our terminology, critical drugs, involved at least potentially in lifesaving situations or in the control of seriously diseased conditions.

Among those, we have taken those which are in solid form, tablets and capsules, and the general feelings based on the state of the art is

that these drugs which are already in solution will be absorbed very rapidly.

Among those which are in solid form, we have given top priority to those which are of relative low solubility, with relative insoluble active ingredients. Those which are highly soluble, those which it has been demonstrated by some of the FDA and Public Health hospitals, are quickly dissolved.

Of the drugs which we feel demand top priority, there are only two or three dozen drugs which will require testing at the outset. This is not an inhuman job by any means, and we are on our way to doing it.

But this job, Senator, will never be completed. Because as soon as a drug comes out from under patent, and it becomes legally possible to make new generics, these will probably have to be looked at in the same way.

I recognize that there is one school of thought which says that we cannot make any statement about generic equivalency or lack of equivalency until we have tested all generics. In a way, this is true. Thus, we cannot say that all the tablets of a particular product meeting USP requirements will meet those requirements, because we have tested only a certain sample—and the only way we could test them all would be to destroy them all—but I think this kind of sampling although it is not 100 percent sure, gives us the practical protection that we require.

Senator NELSON. As I remember it, Dr. Goddard was intending to select x number and complete some kind of a study within the limits of some particular period of time; isn't that correct?

Dr. SILVERMAN. It is our expectation, sir, that the top priority drugs will be completely assayed by 1970.

Senator NELSON. 1970?

Dr. SILVERMAN. Yes, sir.

Dr. LEE. There is one other aspect of this, Mr. Chairman. One is this continuing study which Dr. Silverman has described. And the other is the sampling of drugs in the marketplace to make sure that they do in fact meet the standards, as an additional protection for the consumer of the drugs. The drugs tested will be taken out of pharmacies, drug-stores, and sampled and tested in the FDA laboratory in St. Louis. This will be a continuing surveillance operation to make sure that even with the good manufacturing practices and even with meeting the official standards, that, in fact, in the marketplace the drugs continue to meet the requirement standards.

Mr. GORDON. I have one nitpicking question. You say there are only two or three which demonstrate an initial lack of equivalency and one of them has no practical clinical importance. Are there two or three? Which is it?

Dr. LEE. Dr. Silverman.

Dr. SILVERMAN. There are two. One of them, as you have probably surmised, is chloramphenicol.

Mr. GORDON. There are two, but one has no practical—

Dr. SILVERMAN. The second one is tetracycline. And in the article cited in this publication, the scientists who wrote the article pointed out quite clearly that although differences were detected these were not of any clinical importance.

Mr. GORDON. So we actually come down from the 501 to one?

Dr. SILVERMAN. No, there are two. There are differences which are statistically obvious.

Mr. GORDON. But therapeutically, clinically—

Dr. SILVERMAN. There is one. There was a third which is in a kind of gray zone, and I wouldn't care to state whether this does or does not belong in this category.

Mr. GROSSMAN. One last question: I take it that you have not come to any conclusions yet as to what type—or whether there is a need for a drug formulary, and the relative cost. You talk about costs here sometimes when we were talking about the compendium. I take it that that is separate.

Dr. LEE. That is a separate matter that is still under study and evaluation. When we make the final report to the Secretary as it relates to coverage of prescription drugs under medicare out of the hospital, we will make our final recommendations, as it relates to the formulary.

Mr. GROSSMAN. Do you anticipate that you will make a decision as to a recommendation between the approach taken by Senator Long for a national formulary and that taken in another bill introduced by the minority members of this committee on regional and State formularies?

Dr. LEE. I think we are examining the alternatives with respect to formularies, and the results of ongoing programs using formularies, trying to get as much data as we can on this issue, and the potential cost savings. We will make specific recommendations that will deal with this.

Mr. GROSSMAN. But you weren't implying that the costs would be included in the compendium?

Dr. LEE. The costs, yes, sir; relative costs should be either in the compendium or as a companion publication brought up to date on a regular basis, so that the physician has that information available.

Mr. GROSSMAN. But that is not what you mean by a formulary?

Dr. LEE. No; definitely not.

Mr. GROSSMAN. Thank you.

Senator NELSON. Thank you very much, gentlemen, for your appearance this morning.

Dr. LEE. Thank you very much, Mr. Chairman.

(The Task Force on Prescription Drugs Report previously referred to follows:)

TASK FORCE ON PRESCRIPTION DRUGS

Second Interim Report

and

Recommendations

August 30, 1968

Office of the Secretary
U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Washington, D.C.

(3737)

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UNITED STATES GOVERNMENT

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY*Memorandum*

TO The Secretary

FROM Philip R. Lee, M.D. Assistant Secretary for
Health and Scientific Affairs

SUBJECT Task Force on Prescription Drugs - Progress Report

DATE: August 30, 1968

Prescription Drugs in Medicare

The Task Force has not yet developed definitive recommendations on the possible inclusion of out-of-hospital prescription drugs under Medicare.

We are referring to the Social Security Administration for detailed cost analysis such subjects as program financing, reimbursement methods, and administrative approaches. When this analysis is complete, it will be reviewed by the Task Force and appropriate recommendations prepared for your consideration.

Background Reports

As a result of the work of the Task Force staff and its consultants during the past year, a very large amount of information has been obtained on various aspects of the use, production, and distribution of prescription drug products. Much of this has previously been unavailable, and it is urgently needed by the drug industry, pharmacy, the health professions, consumer groups, Congressional committees, and many Federal and State agencies.

We propose to publish these as a series of background volumes which will serve as the objective basis for many of our recommendations, as well as source material for discussion and further research. It is our plan to publish these volumes on the following subjects:



1. Use of Prescription Drugs by the Elderly
2. The Drug Industry
3. Drug Distribution
4. Drug Prescribing
5. Drug Quality
6. Current Domestic and Foreign Drug Insurance Programs
7. Drug Classification and Coding

Interim Report

I am forwarding with this memorandum the second Interim Report of the Task Force with our findings to date and recommendations.

SUMMARY OF RECOMMENDATIONS

Drug Users

1. The Social Security Administration should expedite the completion of its detailed studies on program financing, program administration, and reimbursement methods for several alternative approaches to the inclusion of prescription drugs under Medicare. (Page 19)

Drug Makers

2. The Department of Health, Education, and Welfare should conduct a continuing survey of drug costs, average prescription prices, and drug use. (P. 36)
3. The Secretary of Health, Education, and Welfare should call one or more conferences with representatives of the drug industry, pharmacy, clinical medicine, and consumer groups to consider--
 - (a) Provision of incentives to the drug industry to invest more research effort in products representing significant improvements to therapy and less in duplicative, noncontributory drug products and combinations. (P. 48)

- (b) Development of a registration and licensing system under which no drug product would be permitted in interstate commerce unless produced under quality control standards set by the Secretary of Health, Education, and Welfare. (P. 48)
 - (c) Limitation of free drug samples to those specifically requested by prescribers, by industry agreement or legislation. (P. 48)
 - (d) Development of more effective methods for ascertaining actual acquisition costs of prescription drugs. (P. 48)
4. The Secretary of Health, Education, and Welfare should call for a joint study by the Department of Health, Education, and Welfare, the Department of Commerce, the Department of Justice, the Federal Trade Commission, and other Federal agencies to consider--
- (a) The substantial differences in the prices at which drug products are offered to community pharmacies and to hospitals and government agencies. (P. 49)

- (b) The substantial differences in the prices at which drug products are offered to American and foreign purchasers. (P. 49)
- (c) Revision of current patent and trademark laws on prescription drugs. (P. 49)

Drug Distributors

- 5. The Congress should enact legislation requiring that the containers of all dispensed prescription drugs be labeled with the identity, strength and quantity of the product, except where this is waived upon specific orders of the prescribers. (P. 53)
- 6. Encouragement should be given to the wider use of prepackage dispensing, in which manufacturers prepare and pharmacists dispense tablets and capsules in precounted form, in sealed, pre-labeled containers, and in such numbers as conform to those most frequently prescribed by physicians. (P. 53)
- 7. The National Center for Health Services Research and Development should develop and support research to improve the efficiency and effective-

ness of community and hospital pharmacy operations. (P. 54)

8. The Bureau of Health Manpower should support--

(a) The development of a pharmacist aide curriculum in junior colleges and other educational institutions. (P. 58)

(b) The development of appropriate curricula in medical and pharmacy schools for training pharmacists to serve as drug information specialists on the health team. (P. 58)

(c) A broad study of present and future requirements in pharmacy, adequacy of current pharmacy education, and the educational changes which must be made. (P. 58)

9. The Health Services and Mental Health Administration should support studies of State laws, regulations, and codes, with priority given to the establishment of model State licensing laws, uniform reciprocity standards, and provisions for the utilization of pharmacy aides. (P. 59)

Drug Prescribers

10. The Department of Health, Education, and Welfare should provide expanded support to medical schools, enabling them to include a course in clinical pharmacology as an integral part of the medical curriculum. (P. 65)
11. The Department of Health, Education, and Welfare should establish or support a publication providing objective, up-to-date information and guidelines on drug therapy, based on the expert advice of the medical community. (P. 70)
12. The Department of Health, Education, and Welfare should support the efforts of county medical societies, pharmacy and therapeutics committees, medical foundations, and medical schools in taking the responsibility for providing continuing education to physicians on rational prescribing. (P. 70)
13. The Secretary of Health, Education, and Welfare should be authorized to publish and distribute a drug compendium listing all lawfully available prescription drugs, including such information as available dosage forms, clinical effects, indica-

tions and contraindications for use, and methods of administration, together with price information on each listed product. (P. 71)

Drug Quality

14. The present clinical trials to determine the biological equivalency of important chemical equivalents should be continued by the Department of Health, Education, and Welfare on a high priority basis. (P. 79)
15. Adequate financial support should be provided to the Food and Drug Administration for necessary educational and inspection operations so that acceptable quality control methods can be instituted and properly maintained in all drug manufacturing and packaging establishments. (P. 81)
16. The Food and Drug Administration should be authorized to provide additional support, including grants-in-aid, to State and local agencies in order to improve quality control of prescription drugs in intrastate commerce. (P. 82)

Ongoing Programs

17. The Federal Interdepartmental Health Policy Council should concern itself with the coordination of all ongoing Federal prescription drug purchase and reimbursement programs. A special subcommittee of the Council should be appointed for this purpose. (P. 103)

Classification and Coding

18. The Department of Health, Education, and Welfare, the Department of Defense, and the Veterans Administration should test the proposed drug classification system to determine the feasibility of its eventual use in all public and private drug programs. (P. 105)
19. (a) An appropriate identifying code number should be made part of all drug labels, package inserts, catalogs and advertising. (P. 107)
- (b) An appropriate coding system should be developed and tested by government and industry for this purpose. (P. 107)
- (c) After consideration of the results of this test, appropriate legislation should be introduced to require coding of all drug

products in interstate commerce. (P. 108)

20. The drug code adopted by government and industry should be utilized in the National Drug Code Directory. (P. 108)

Utilization Review

21. The National Center for Health Services Research and Development, in cooperation with State and local medical groups, community pharmacies, hospitals, and consumer groups, should support pilot research projects on prescription drug utilization review methods. (P. 110)

TERMINOLOGY

The term generic equivalents is not used in this report. It has been widely used, but has been given so many different interpretations that it has become confusing.

Instead, the following terms are utilized:

Chemical equivalents - Those multiple-source drug products which contain essentially identical amounts of the identical active ingredients, in identical dosage forms, and which meet existing physico-chemical standards in the official compendia.

Biological equivalents - Those chemical equivalents which, when administered in the same amounts, will provide essentially the same biological or physiological availability, as measured by blood levels, etc.

Clinical equivalents - Those chemical equivalents which, when administered in the same amounts, will provide essentially the same therapeutic effect as measured by the control of a symptom or a disease.

The following terms are also utilized:

Generic name - The established or official name given to a drug or drug product.

Brand name - The registered trade-marked name given to a specific drug product by its manufacturer.

Molecular "manipulation" - A minor modification in the molecular structure of a chemical, yielding a new and patentable product.

"Me-too" or "duplicative" drug - A new drug, often made by means of molecular manipulation, which offers no significant therapeutic advantage over a related drug already on the market. (Chemical equivalents, since they are chemically identical, are not considered to be "me-too" products.)

Rational prescribing - Prescribing the right drug for the right patient, at the right time, in the right amounts, and with due consideration of relative costs.

INTRODUCTION

Since the Task Force on Prescription Drugs was formally established in June of 1967, members of the Task Force staff in cooperation with many governmental and nongovernmental consultants have examined various important aspects of drug production, distribution, and use.

These studies have included the health needs and prescription drug use of the elderly and other groups, the prescription drug industry, the drug distribution system, the prescribing patterns of physicians, drug quality, ongoing drug insurance programs in the United States and other countries, drug classification and coding, and drug utilization review.

Findings from these studies have been considered by the Task Force, and are summarized in the following sections, together with recommendations for action.

These proposals are not concerned with any specific drug program. They are directed toward producing the highest possible quality of health care, at the lowest practical cost, for all people.

THE DRUG USERS

The elderly in the United States--those aged 65 or more--represent only a relatively small proportion--about 10 percent--of the total population of this country.

But their inordinate health needs, their high health care costs in general and high drug costs in particular, and their limited financial resources combine to create a serious and sometimes a devastating medical and economic problem far out of proportion to their numbers.

For many elderly people, illness serves as a major cause of their poverty by reducing their incomes, while poverty serves as a major contributory cause of illness by making it impossible for them to obtain adequate health care.

Yet it is not only the totally impoverished or the totally incapacitated who are in a precarious position. There are many elderly men and women who have some income and some savings--who may even have sufficient Medicare or other insurance to protect them against the bulk of hospital and medical costs of a brief illness--but who cannot pay for the out-of-hospital drugs and other costs of a long-continuing chronic illness without

seeing their financial assets eroded or totally dissipated.

Numbers and Health Needs of the Elderly

There are now more than 19 million Americans over the age of 65. Among them, about 57 percent are women and 43 percent are men. This disproportion in sex distribution has been increasing steadily since about 1930--a trend of importance in any prescription drug study, since the use of these drugs by women is significantly higher than that by men.

In connection with the elderly, the term aging has often been considered synonymous with illness. There is, in fact, no necessary relationship between the two, but it is undeniably a fact that illness strikes the elderly far more frequently than it does younger age groups.

Approximately 80 percent of the elderly--in comparison with 40 percent of those under 65--suffer from one or more chronic diseases and conditions.

Arthritis and rheumatism afflict 33 percent; heart disease, 17 percent; high blood pressure, 16 percent; other cardiovascular ailments, 7.5 percent; mental and nervous conditions, 10.5 percent; hearing impairments, 22 percent; and visual problems, 15 percent.

Many of these conditions can be controlled or alleviated by modern medical care, especially by the proper use of drugs. This is reflected in the heavy expenses of the elderly for health care, and particularly in their heavy expenses for drugs.

Health Expenditures

Between 1950 and 1966, total national expenditures for health services and supplies--including hospital costs, physicians' fees, and drug costs--rose from \$11.9 billion to \$41.8 billion. (Per capita expenditures increased from \$78.20 to \$212.47.)

In that same period, expenditures for out-of-hospital prescription drugs rose from \$1.0 billion to \$3.2 billion. (Per capita expenditures increased from \$6.85 to \$16.05.)

The increase in drug expenditures has resulted in part from a greater number of prescriptions per individual--an average of about 2.4 acquisitions per capita in 1950 and 4.6 in 1966--as well as from a significant rise in the average cost of prescriptions.

In 1950, a number of independent surveys reported the average cost of all prescriptions at the retail level was between \$1.66 and \$2.03. In 1966, independent

surveys estimated the average was between \$3.26 and \$3.59. A special study conducted for the Task Force showed that the average prescription cost for the elderly in 1966 was even higher--\$3.91.

Distribution of Drug Expenditures

If drug use were equally distributed among all groups--that is, 4 to 5 prescriptions per year at a cost of \$3 to \$4--there would be no major problem for the elderly. But this is far from the actual situation.

Although the elderly represent slightly less than 10 percent of the total population, they account for about 23 percent of all prescription drug expenditures.

A nationwide study by the National Center for Health Statistics in fiscal year 1965 showed the following (see Table 1):

- The average number of acquisitions--i.e., the number of prescriptions or refills--for the elderly was more than twice that for the total population, and nearly three times that for those under 65.
- The average number of acquisitions for elderly women was nearly 50 percent more than the number for men.

Table 1

Average Number of Acquisitions and Annual Cost of Prescribed Drugs, per
Person by Selected Characteristics, Fiscal Year 1965

<u>Characteristics</u>	<u>No. of Acquisitions</u> ^{a/}			<u>Annual Cost</u>		
	<u>All Ages</u>	<u>Under 65</u>	<u>65 and Over</u>	<u>All Ages</u>	<u>Under 65</u>	<u>65 and Over</u>
All persons	4.7	4.0	11.4	\$15.40	\$12.77	\$41.40
Sex						
Male	3.7	3.1	9.3	12.00	9.88	34.70
Female	5.6	4.8	13.1	18.60	15.49	46.70
Color						
White	4.9	4.2	11.5	16.40	13.62	42.60
Nonwhite	3.1	2.7	10.2	7.80	6.57	26.90
Geographic Region						
Northeast	4.4	3.8	10.6	13.30	10.80	37.00
North Central	4.4	3.8	10.9	15.00	12.37	39.90
South	5.3	4.5	13.6	17.50	14.64	47.40
West	4.3	3.7	9.7	15.30	12.93	40.00
Disability - Men						
None				14.80		19.40
Mild				33.50		40.90
Moderate				33.60		40.80
Severe				71.70		71.00
Disability - Women						
None				23.20		34.00
Mild				50.00		64.40
Moderate				63.40		67.60
Severe				101.40		94.70

a/ New prescriptions or refills.

- The per capita expenditure for prescription drugs for the elderly was almost three times greater than that for the total population, and more than three times greater than that for those under 65.
- The per capita expenditure for elderly women was more than one-third higher than that for elderly men.
- The per capita expenditure for the elderly with severe disabilities was nearly three times greater than that for those with no disabilities.

In general, the survey showed, total prescription drug expenditures in all age groups were higher for women than for men, for whites than for nonwhites, and for those in the South and West. The higher expenditures for whites appear to be a reflection of their greater affluence--their greater ability to seek medical care and to afford drugs rather than greater health needs. The high cost in the South appear to be related to exceptionally heavy utilization, while in the West they reflect lower utilization but much higher costs per prescription.

Similarly, although the burden of drug costs falls most heavily upon the elderly, it does not fall evenly upon these individuals.

A 1968 estimate, for example, indicates that 20 percent of the elderly will have no drug expenses, while the costs will be less than \$50 for 41.5 percent, between \$50 and \$99 for 19 percent, between \$100 and \$249 for 15.5 percent, and \$250 or more for 4 percent.

A recent investigation, carried out on a limited group in Pennsylvania, indicated that, among the elderly who actually obtained prescription drugs, about 2 percent accounted for about 21 percent of the total cost, and about 10 percent of the individuals accounted for about 47 percent of the cost.

Financial Resources of the Elderly

The size of drug bills for the elderly represents only one phase of the problem. Intimately related is their ability to pay those bills.

Since July 1, 1966, implementation of the Medicare program has substantially increased the ability of many elderly men and women to meet their doctor and hospital bills, not entirely but in large part. Expenditures for

out-of-hospital prescription drugs, however, are not covered by the present Medicare law, and it has been necessary for elderly patients to utilize other sources.

Income. In 1966, half of the families headed by an elderly individual had total incomes--including Social Security payments--of less than \$3,645, or \$70 a week. For elderly men and women living alone, or with someone not a relative, more than half had incomes of less than \$1,500, or about \$30 a week.

Assets. Recent studies have shown that the average per capita amount of savings and other assets held by the elderly is about \$15,000.

But 30 per cent of the elderly have assets of less than \$1,000 apiece. For them, a serious illness could wipe out their meager savings in a few months.

Health Insurance. Health insurance through Blue Cross, Blue Shield, commercial insurance companies, group practice plans and other organizations is available to many of those over the age of 65, but provision of prescription drugs--except to hospitalized patients--is limited.

Where out-of-hospital drug expenses are covered, these are generally included in major medical policies involving deductibles of \$100, \$250, or \$500--useful only in so-called "catastrophic" illnesses.

Recently, drug insurance programs have been developed to provide adequate coverage of out-of-hospital drug costs, but membership in the plans is usually limited to members of employed groups, and few of these are in the older-age group.

Tax Relief. To the extent that expenses for drugs are included as deductions on income tax returns, reduced income tax payments represent a source of payment for these drugs.

For the elderly, such relief obtained through Federal income tax deductions has been estimated to represent about 9 percent of drug expenditures. But these savings benefit only those elderly individuals who receive enough income to require income tax payments, and would be of little importance to those with low incomes.

Free Drugs. From the 1964-65 study of the National Center for Health Statistics, it appears that about 3 percent of the elderly received their drugs at no cost

from their physicians.

Public Assistance. About 6 percent in 1964-65 obtained prescription drugs from State or local welfare agencies or similar sources. The provision of free drugs through welfare agencies--under Medicaid or other Federal, State or local programs--may solve the problem as it directly affects some of the elderly. The basic economic problem is not solved, however, but merely shifted from the elderly to the taxpayers.

Out-of-Pocket Costs. In enabling the elderly to meet their out-of-hospital prescription drug expenses, the combined impact of insurance coverage, tax relief, free drugs, and public assistance does not seem to be substantial, covering only about 20 percent of total costs.

The remainder--about 80 percent--must be met by out-of-pocket expenditures from income and assets. For those over 65, these financial resources are rarely substantial.

Thus, the elderly, with limited income, limited savings, and minimal protection from health insurance and other sources, are obliged to face the burdens of drug costs which are far heavier on a per capita basis than those which weigh on their fellow citizens, who in most

cases are younger, healthier and wealthier.

Patterns of Drug Use by the Elderly

Essential for an effective attack against the drug problems of the elderly are detailed, objective data on the drugs they actually use and the costs of these prescriptions.

In 1966, for example, the elderly obtained about 198 million out-of-hospital prescriptions from community pharmacies at a total retail cost of \$852 million, involving many thousands of different drug products. ^{a/} But this knowledge is not enough.

It is necessary to know--

--which drugs, by brand or generic name, were dispensed for the elderly.

--which were utilized most frequently;

--which diseases accounted for the greatest drug utilization;

--which drugs were most frequently involved in long-term maintenance therapy;

^{a/} An additional 26.9 million prescriptions, at a cost of \$104.7 million, were obtained from hospital and mail order pharmacies and other sources.

- how much each of these drugs cost at the wholesale level, and at the retail level; and
- to what extent drug costs could be reduced if low-cost chemical equivalents were used wherever they were available.

To obtain the needed information, the Task Force requested the Public Health Service to undertake a special study, with major responsibility assigned to the Health Economics Branch of the Division of Medical Care Administration, and assistance provided by other agencies within the Bureau of Health Services, and by the Food and Drug Administration.

This project--probably the first of its kind ever undertaken--was aimed at developing a master list of the drugs which were most frequently prescribed and dispensed for the elderly in 1966, ^{a/} and which would account for about four-fifths of their drug use during that year.

^{a/} 1966 was selected as the study year, since it represented the most recent period for which essentially complete data were available for Task Force analysis beginning in June 1967.

The Task Force Master Drug List. As developed for the Task Force, the Master Drug List (MDL) contained the 409 most frequently prescribed drugs dispensed to the elderly in 1966. These accounted for 174.7 million, or 88 percent, of all prescriptions dispensed by community pharmacies for the elderly in that year, and for \$682.3 million, or 80 percent, of their prescription drug costs at the retail level. ^{a/}

The complete MDL, with a variety of analyses, will be presented in a separate background paper.

Included among the 409 products were 379 which were dispensed under their brand names. These accounted for more than 90 percent of the total number of MDL prescriptions, about 90 percent of the total acquisition cost to retailers, and 95 percent of the total retail cost to the patients.

^{a/} It should be noted that insulin, which has figured prominently in many drug insurance programs, is not included in these tabulations, since it is generally dispensed without a prescription. In 1966, it was estimated that insulin dispensed to the elderly cost about \$3 million at the retail level.

Among these were 87 products which were dispensed under their brand names, but for which chemical equivalents were available--often but not always at lower cost--and could have been prescribed under generic names. They accounted for about 29 percent of the total number of prescriptions, 27 percent of the total acquisition cost to retailers, and 27 percent of the retail cost to patients.

Also included were 30 drugs which were dispensed under their generic names. They accounted for about 10 percent of the number of prescriptions, 10 percent of the total acquisition cost, and 5 percent of the total retail cost.

Average Prescription Cost. For all 409 MDL drugs, the average cost per prescription was \$3.91. For the 379 drugs dispensed under brand name, it was \$4.11. For the 30 drugs dispensed under generic name, it was \$2.02.

Most Widely Used Drugs. The 10 most frequently used products--headed by an oral antidiabetic agent, and including two tranquilizers, two diuretics, an analgesic, an anti-arthritic agent, a cardiac drug, and two sedatives--accounted for 20 percent of the total number of MDL prescriptions, 21.6 percent of the total acquisition cost to

retailers, and 20.7 percent of the total retail price to consumers.

Only two of these were available from several manufacturers under a generic name.

Approximately 50 percent of the total cost to patients was represented by the top 29 drugs, which also represented 53 percent of the total number of prescriptions and 49 percent of the total acquisition cost to retailers. Among these were 18 drugs which could be obtained only under a brand name from a single supplier, eight which were dispensed under a brand name although a chemical equivalent was available, and three which were dispensed under generic name.

Therapeutic Category. Cardiovascular preparations--including vasodilators, digitalis and its congeners, and hypotensive drugs--accounted for 38.9 million, or 22 percent, of the total prescriptions, and \$157.8 million, or 23 percent, of the total retail cost to consumers.

Tranquilizers, with 16.9 million prescriptions at a total cost of \$78.9 million, rated second, followed by diuretics, with 16.0 million prescriptions at \$62.6 million; and sedatives, with 15.1 million prescriptions at \$32.3 million.

These four categories together represented about one-half of all prescriptions for products in the MDL, and 49 percent of the total cost to patients.

Antibiotics ranked fifth, including 13 million prescriptions at a retail cost of \$64.3 million.

Diagnostic Category. About 66.2 million, or 38 percent, of the total prescriptions, at a cost of \$244.3 million, or 36 percent, of the total retail cost, were used for the treatment of heart disease and hypertension.

An additional 17.3 million prescriptions, at a retail cost of \$65.4 million, were applied for the control of arthritis and rheumatism.

About 11.6 million prescriptions, at a cost of \$47.4 million, were dispensed for the treatment of mental and nervous conditions.

Together these groups accounted for 95.1 million, or 54 percent, of the total MDL prescriptions, and \$357 million, or 52 percent, of the total cost to consumers.

Maintenance Therapy. A sizeable proportion of out-of-hospital drugs prescribed for the elderly are so-called long-term maintenance drugs, used primarily for the control of chronic diseases. Few of these --

at least at the present state of knowledge--can be cured, but in many instances appropriate drug therapy will enable the patient to live a reasonably comfortable and productive life.

Among the 409 drugs in the MDL, 71 were prescribed for 30 to 59 days during the year, 42 of them for 60 to 89 days, and 78 of them for 90 days or more.

These last 78 accounted for only about 20 percent of all MDL products, but they represented 59.6 million, or 34 percent, of all MDL prescriptions, and \$242 million, or 35 percent, of total costs to the consumer. More than half of them were for the control of cardiovascular disease.

We find, therefore, that the requirements for appropriate prescription drug therapy by the elderly are very great--far greater, in fact, than those of any other group--and that many elderly men and women are now unable to meet these needs with their limited incomes, savings, or present insurance coverage. Their inability to afford the drugs they require may well be reflected in needless sickness and disability, unemployability, and costly hospitalization which could have been prevented by adequate out-of-hospital treatment.

With steadily increasing prescription expenditures, this problem is destined to become increasingly serious.

The Task Force therefore recommends that the Social Security Administration should expedite the completion of its detailed studies on program financing, program administration, and reimbursement methods for several alternative approaches to the inclusion of prescription drugs under Medicare.

The Task Force defers any definitive recommendation on the possible inclusion of out-of-hospital prescription drugs under Medicare until the completion of these studies.

THE DRUG MAKERSThe Industry

Total drug sales--prescription and nonprescription drugs alike--have increased substantially in the last decade, rising from nearly \$3 billion in 1957 to about \$5 billion in 1967 at the manufacturer's level. Prescription drugs accounted for about two-thirds of this volume.

Foreign drug sales by American companies exceeded a billion dollars in 1967.

Approximately 95 percent of the prescription drug sales were made by the 136 member companies that comprise the Pharmaceutical Manufacturer's Association (PMA). Members of the PMA produce and sell both brand name and generic name products. Just as they account for the overwhelming proportion of sales, they conduct essentially all of the industry's research, they control the overwhelming proportion of drug patents, they conduct the most vigorous promotion of their products, they compete vigorously--usually on the basis of innovation and quality and rarely on the basis of price--for the favor of the medical profession, and they achieve the industry's highest rates of profit.

The remaining five percent of the Nation's prescription drugs are manufactured by many hundreds of companies, and are sold under both trademarked and generic names. The total number of such firms is believed to be more than 700. They control few drug patents, do little or no research, compete on the market on the basis of both quality and price, conduct only minimal promotion of their products, and achieve relatively low rates of profit.

Research and Development

Various Federal agencies support drug-related research and development at the rate of more than \$100 million a year. In addition, other studies included in the Federally-supported biomedical research program may be expected to have eventual implications for drug research and development.

The drug industry's research and development program is now nearly \$500 million a year, almost all conducted by about 70 of the PMA members.

The industry's research effort has been noteworthy in many respects --

- New drugs developed through research have given physicians remarkable weapons for the improved treatment of infections, metabolic disorders, arthritis, heart disease, high blood pressure, and a host of other crippling or deadly diseases.
- Based on percentage of sales, the drug industry's investment in research is about three times greater than that of any other major industry.
- The number of new products has been impressive. For example, between 1957 and 1968, 311 products introduced on the market were described as important new single entities. They represented about 15 percent of the 2,131 new prescription drug products introduced during that period. Also included were 1,440 products containing two or more older drugs in a new combination, and 380 drugs which were essentially duplicates or minor modifications of products already in use.

--The annual number of important new entities, those which represent significant advances, reached a peak in 1958--four years before the Kefauver-Harris Drug Amendments of 1962--and decreased steadily until 1967, when the number started to rise again.

Also impressive is the vigor and frequency with which industry spokesmen have said that any government interference in their operations may force them to reduce their research programs.

The Task Force is convinced that the directions and quality of some industry research programs deserve careful consideration.

We have noted the serious and increasing concern expressed by practicing physicians, medical educators, pharmacologists, and economists--and even some industry leaders--at the number of molecular modifications of older drugs introduced each year. Some of these modifications undoubtedly represent significant advances, but most appear to be so-called "me-too" drugs--substances which are not significantly different from other drugs, nor significantly

better, and represent little or no improvement to therapy, but which are sufficiently manipulated in chemical structure to win a patent.

We have noted the comparable concern expressed at the number of new fixed combinations of old drugs introduced each year. Although these combinations may offer some convenience to elderly patients in particular, clinicians and pharmacologists have cautioned that they also involve obvious hazards and combine drugs in a "locked-in" proportion which may or may not fill the needs of individual patients.

The numbers of duplicative and combination drug products introduced in recent years have been decreasing, but they still represent the great majority of all so-called new drugs.

It is evident that these duplicative products, along with combination products, are used widely by some physicians, perhaps on the basis of the industry's exceedingly effective marketing and promotion activities. But it is also evident that the need for this over-abundance of drug products has not been convincing to some medical experts.

In many of the Nation's leading hospitals, when expert physicians have served on pharmacy and therapeutics committees to select the drugs needed for both inpatient and outpatient therapy, they have generally found many if not most of these duplicative drugs and combinations to be unnecessary. These products have been found generally unnecessary by physicians providing medical care to the armed forces. They have been found generally unnecessary by leading clinical pharmacologists.

If these items were offered at prices substantially lower than the products they duplicate, they would provide at least an economic advantage, but in most instances they are introduced at the same or even higher prices.

The development of such duplicative drugs or combination products cannot be considered an inexpensive fringe benefit. Each requires laboratory research, clinical trials, and the accumulation of sufficient data to demonstrate to the Food and Drug Administration that the new product--although it may not represent any significant therapeutic advance--is at least safe and efficacious.

Since important new chemical entities represent only a fraction--perhaps 10 to 20 percent--of all new products introduced each year, and the remainder consists merely of minor modifications or combination products, then much of the industry's research and development activities would appear to provide only minor contributions to medical progress.

The Task Force finds that to the extent the industry directs a share of its research program to duplicative, noncontributory products, there is a waste of skilled research manpower and research facilities, a waste of clinical facilities needed to test the products, a further confusing proliferation of drug products which are promoted to physicians, and a further burden on the patient or taxpayer who, in the long run, must pay the costs.

A solution to this problem requires joint efforts on the parts of industry and the Federal Government (see page 47).

Quality Control

Any company, large or small, brand name or generic name producer, can institute and maintain an effective

quality control program, and most companies have apparently done so. The cost of such a program has been estimated to be about 2.4 percent of sales for a large company, but may be somewhat more for a smaller firm.

On the other hand, not all companies have maintained adequate quality control, and their products have had to be recalled--either voluntarily or by government order--for such defects as mislabeling, subpotency, or contamination. These recalls have involved both large and small firms, and both brand name and generic name products.

Several hundred such violations are reported each year. Investigations have often indicated that these are related to the failure of a manufacturer to comply with what are known as Good Manufacturing Practices, including such factors as plant sanitation, personnel surveillance, equipment maintenance, raw material standards, record keeping, and quality checks at every appropriate stage of manufacture and packaging.

The Task Force believes that this situation may be substantially improved by the intensified inspection program now being developed by the Food and Drug

Administration. At the same time, it believes that further study is warranted of the alternative proposal that a registration and licensing system be established under which no drug product would be permitted in interstate commerce unless produced under quality standards set by the Secretary of Health, Education, and Welfare, (see page 47).

Marketing

For those major companies which have presented any data, marketing expenses--including particularly those for advertising and promotion--represent from about 15 to 35 percent of sales. Such expenses for generic name products appear to be substantially lower than those for brand name products.

Industry spokesmen have claimed that marketing is an accepted part of any business activity; that their marketing costs are reasonable; and that their marketing efforts--including advertising, direct mailings, and personal visits by detail men to physicians--are primarily educational in nature. They have claimed that the promotional aspects of drug marketing are a mark of the intense

competition in the industry.

On the other hand, critics have asserted that intensive promotional efforts may be acceptable to sell such products as detergents, beer and used automobiles, but not for such vital necessities as prescription drugs; that the expenses for drug marketing are excessive and add needlessly to the cost of prescriptions; that prescription drug advertising and other promotion has reached the proportions of supersaturation; and that some has been --at least until recent regulations were established by the Food and Drug Administration--inaccurate, unscientific and biased.

It appears evident to the Task Force that drug promotional activities are related to the particular type of competition which unquestionably exists in the prescription drug industry, among others--an intense competition between companies, with the promise of a greater share of a relatively limited market and richer profits for the successful competitor--but that these activities have little to do with normal price competition in the

retail marketplace--with the promise of eventual price savings to the consumer.

The Strategy of Names. Intimately related to marketing, and the competition between brand and generic products, is the subject of brand and generic names.

In the past, whether fortuitously or by design, most generic names--though certainly not all of them--have been relatively long, complicated and difficult to pronounce and remember.

During the past year, this situation has improved somewhat as the result of new policies established by the U.S. Adopted Names Council, but more improvement is needed.

The Task Force commends the Council for its efforts toward simplifying generic names and urges that these efforts be continued and strengthened.

Advertising and Promotion. Included among the promotional activities of some major prescription drug companies have been the support of scientific or medical conferences or symposia totally unrelated to any commercial product; the publication of educational materials for the public on such subjects as prevention of narcotic and drug abuse,

immunization campaigns, and school health; the establishment of scholarships and fellowships, especially for the benefit of underdeveloped countries; and the no-strings-attached support of some scientific and medical societies.

These and similar activities are held in high esteem in the scientific and medical community, and are recognized as significant contributions to the improvement of public health.

Also included among promotional activities is the drug advertising in medical journals, direct mailings, throw-away publications, and others which has long since reached astounding proportions. It is estimated that the major drug companies together now spend some \$3,000 per physician annually to reach each of the nearly 200,000 physicians who represent the target audience--those who will decide for which drug product their patients should pay.

Significantly, this advertising rarely if ever mentions price.

Unquestionably, much of this material is accurate and educational. The frequency of biased, inaccurate drug

advertising has apparently been reduced since the enforcement of new advertising regulations by the Food and Drug Administration began in 1967. But the overall value of such advertising volume continues to be seriously questioned.

Similarly, the potential impact of these large advertising expenditures on the editorial policies of the journals which are supported in large part by drug advertisements appears to deserve careful study.

Detail Men. Major brand name manufacturers--and a few generic name companies--employ about 20,000 representatives to call on physicians, hospitals, and pharmacists, and provide information on their products.

Whether such activities may be described as primarily promotional or primarily educational is difficult to determine. It is doubtful, however, that physicians can expect such detail men to give invariably unprejudiced and objective advice.

Significantly, the presentations of detail men rarely include mention of price.

Free Samples. Free drug samples have customarily been distributed to physicians without request to induce them to try a product and test its advantages on their own patients. But few physicians are able to undertake any serious trials of this nature. Furthermore, if a physician does try a drug, in most instances he can do so with only a very few patients; the possibility that such a limited study can serve as a basis for a scientific judgment seems to be small.

Free drug samples have made it possible for physicians and hospitals to supply drugs at no cost to some indigent patients. This need, however, has been modified by the advent of Medicaid and other programs under which Federal and State welfare funds may be used to provide drugs to eligible patients.

It has been reported that free samples have been involved in accidental poisonings, drug abuse, and black market activities.

Some major drug manufacturers have reacted to this problem by distributing free samples only to those prescribers who have specifically requested them. It

appears that further steps in this direction call for joint efforts by the industry and the Federal Government (see Page 47).

Industry Prices

Few aspects of the drug industry are more confused--or more confusing--than its pricing structure. Ostensibly, wholesale prices are listed in company catalogs and price lists, but these generally represent maximum prices. These serve merely as an umbrella beneath which actual prices are set by quantity discounts, hospital discounts, government discounts, two-for-the-price-of-one deals, rebates, and other special arrangements.

With many Federal, State and private drug programs now using reimbursement formulas based on wholesale costs to the vendor, there is need for developing an efficient system to ascertain actual acquisition costs. This calls for cooperation among manufacturers, wholesalers, vendors, insurance companies, and governmental agencies (see page 47).

Price Indices. Particular confusion has resulted from the comparison of various indices intended to indi-

cate the trend of drug costs.

From the Consumer Price Index of the Bureau of Labor Statistics, it is obvious that retail drug prices have been decreasing steadily since about 1958.

From three independent surveys, it is equally obvious that these prices have been increasing during the same period.

The disparity is based on the fact that the indices are measuring different things.

The BLS index is aimed at measuring the change in a relatively fixed "market basket" of about a dozen selected drug products. During the past decade, the prices of these items have, on the average, decreased. The items selected for the "basket," however, do not accurately represent the most widely used drugs, and they do not reflect the changes in consumer expenditures which constantly occur when new and more costly products are introduced on the market and replace less costly products.

On the other hand, the independent surveys are not concerned with the price changes of any individual drug products, but instead are aimed at determining the average

price of the prescriptions which people do purchase. All three of these surveys show a definite upward trend in the average cost of these prescriptions, but they do not agree in the extent of increase because of different sampling methods.

We find there is need for information on actual drug costs, expenses and utilization by the elderly and other groups.

Accordingly, we recommend that the Department of Health, Education, and Welfare should conduct a continuing survey of drug costs, average prescription prices, and drug use.

Hospital and Government Discounts. Many drug manufacturers customarily offer their products to hospitals at prices substantially lower than those available to community pharmacists. The savings are not necessarily reflected in lower drug prices to hospital patients.

To a considerable extent, these hospital discounts represent a subsidy to hospital patients--or, more often, to the hospitals themselves--at the expense of non-hospitalized patients.

Spokesmen for some pharmacy associations have urged that wholesale prices to hospital pharmacies and community pharmacies be kept at the same level--a move which would lower prices moderately to community pharmacies, but raise them substantially to hospital pharmacies. Hospital spokesmen have declared any such action would raise hospital per diem rates still higher.

Similar differences are apparent between the prices of drugs sold to community pharmacies and those sold to Federal and State agencies.

The Task Force finds that the substantial differences in the prices at which drug products are offered to community pharmacies and to hospitals and governmental agencies deserve further examination (see page 49).

Foreign Prices. Many American companies offer their products for sale in foreign countries at prices substantially below those available in the United States, primarily to meet price competition which does not generally exist in this country.

During the past few years, there has been mounting insistence that these companies should price their

products essentially the same in all countries.

The drug companies have countered that any increase in their foreign prices would drive them out of the foreign markets, not only reducing their earnings but upsetting still further this country's unfavorable balance of trade. On the other hand, any attempt to reduce American prices to the level of prices on foreign markets could be catastrophic to their total financial structure.

The Task Force finds that further study is required on the different prices at which drug products are offered to American and foreign purchasers (see page 49).

Patents, Trademarks and Competition

In the case of most commodities, rival companies compete vigorously on the open market on the basis of both quality and price, with the consumer having the right to make the final judgment. In most instances, the results have been steadily increasing quality and decreasing price.

In the case of drugs, there are distinct differences. The competition is based almost entirely on real or presumed therapeutic advantages. The patient, who must pay for the drug, rarely has any voice in its selection. The

decision on which product the patient must buy is made by the physician. Although moderate or even enormous price differences may exist between products of comparable quality, this is seldom brought to the physician's attention.

Some have attempted to justify this situation by describing the physician as the patient's expert purchasing agent. In the view of the Task Force, this concept is not valid; in most situations, a purchasing agent who purchased without consideration of both quality and price would be unworthy of trust.

In what has been described as this "new competition" in the drug business, patents and trademarks have played key roles.

On the one hand, industry supporters have insisted that the present patent and copyright system makes possible the incentives and rewards that are essential for the industry's large research and development effort, the flow of new products to which it leads, the subsequent benefit to health, and the ready identification of brand name products.

On the other, it has been asserted that drug patents, combined with multi-million-dollar drug advertising campaigns, can keep new or small companies out of the high-profit circle, and effectively stifle price competition in the marketplace.

Various proposals to modify the patent system have been considered by the Task Force.

Abolition of Drug Patents. Removal of all patent protection from new drugs, it appears, would be a destructive move. Virtually all the important new drugs of recent years have come from countries providing patent protection. Few, if any, have come from Eastern European nations which offer little or no patent protection. Several important drugs have originated in Italy, which does not provide patent protection, but these have been quickly patented in foreign countries.

Restricted Patent Life. It has been estimated that a company will usually recoup all its research and development costs within about three years after it reaches the market. Accordingly, it has been proposed that the patent on a drug should be reduced from the

present period of 17 years to a much briefer period--such as 10 years, 7 years, or even 5 years.

It has been shown, however, that requirements to establish the safety and efficacy of a new drug may take many years of effort--perhaps as many as seven years. Where such testing continues after a patent is issued, the period of actual patent protection may be less than the statutory 17-year period.

Co-Terminal Patents and Trademarks. It has also been recommended that the patent life on a drug be maintained at the present 17 years, but that exclusive rights to the trademark should last no longer than the patent. Thus, at the end of the 17-year period, any qualified manufacturer would be free to market the drug under its original trademark or brand name.

Generic Name Only. A related proposal is that new drugs should be marketed only under a generic name--exclusively by the inventor until the patent expired, and then by any manufacturer who desired to produce it. Used with the generic name would be the name of the manufacturer, to identify the source of the product. This would

clearly tend to minimize the confusing multiplicity and complexity of names put before physicians and would better identify the nature of the drug.

Compulsory Licensing. Unlike the United States, many countries have provisions under which the government may require the patent holder to license other manufacturers through a suitable royalty system. These provisions have rarely been enforced, perhaps because realistic price competition exists in the marketplace and lower prices may be invoked through negotiations.

Proponents of such legislation in this country have argued that if licensing were required after the first three years of a product's market life--i.e., after major recovery of research and development costs--other firms could enter that product market by paying royalties, and price competition might then occur among these rivals. Beneficial results to consumers would be possible only for those products with a commercial life longer than three years. For such products, the patent holder would continue to earn an innovator's profits, though perhaps at lower rates than before, and consumers possibly could

purchase prescriptions at lower price levels.

Make-or-Sell Licensing. As yet another approach, it has been proposed that the patent holder should not be permitted to monopolize both the manufacture and the sale of a new drug, but should be required to license either other producers or other sellers.

We note that these and other proposals to amend patent and trademark laws on drugs have been considered in the United States and other countries, and believe further study is necessary (see page 49).

Profits and Risks

In a free enterprise system, it is obvious that a company must make a profit. Unless it achieves this primary objective, it cannot stay in business.

Ample evidence is available to demonstrate that the drug industry has been able to stay in business. It has maintained an annual profit rate based on net worth which is substantially above that of the average of major American industries.

--One study of 41 industries has shown that,
between 1956 and 1966, the drug industry never

ranked lower than third on the basis of after-tax income as a percentage of net worth. In six of those years, it ranked in first place.

--Another study showed that, among 31 major industries, drug makers have averaged an 18.1 percent return on capital, as compared with 9.7 percent for the whole group.

A similar high rate of profit for the drug industry is indicated on the basis of profits calculated as a percentage of sales.

Spokesmen for the drug industry have agreed that its profitability is above average. They say, however, that this high rate is necessitated by the high degree of risk in the industry, and the need to attract the capital to finance further growth.

The Task Force has been unable to find sufficient evidence to support the concept of the drug industry as a particularly risky enterprise.

There is abundant evidence that the development of an individual drug may be associated with a high degree of risk, and that any such development is an economic as

well as a scientific gamble. There is, however, no evidence that this kind of risk characterizes a typical major drug company with a substantial line of drug products. When such a company undergoes a painful loss in this kind of a gamble, the record would seem to show, it generally covers it by substantial profits on other drugs.

The record would also tend to show that--at least during the past 20 years--losses of this nature have driven few if any major pharmaceutical manufacturers into serious financial straits.

In recent years, some major American drug manufacturers have diversified their operations by moving into other operations. In some instances, this has been described as an attempt to minimize risks. At the same time, however, it is apparent that other companies are diversifying their operations by moving into the drug field.

The Chief Economist of the Federal Trade Commission has testified that, on the basis of advice given by investment analysts, there is no reason to conclude that the drug industry is a uniquely risky industry. In fact,

it appears that large drug companies should have little difficulty obtaining adequate capital for growth should they choose to go into the market for it. Actually, however, their earnings are large enough to preclude the frequent need for equity capital.

If new Federal regulations concerning drug safety, drug efficacy, and drug advertising have had any significant effect in reducing drug profits, this is not evident in recent drug company profit statements.

The "Reasonableness" of Drug Prices

Whether prescription drug prices set by the major manufacturers are "too high," "reasonable," or "too low" is obviously a problem which cannot be resolved to the mutual satisfaction of all manufacturers and all consumers.

It appears, however, that current drug prices at the manufacturer's level are marked by these characteristics:

1. They reflect research and development costs which are relatively high in comparison with other industries, and which include a substantial degree of effort yielding only duplicative or "me-too" drugs and combination products that

contribute little to the improvement of health care.

2. They reflect promotion efforts which are high and are directed primarily to physicians.
3. They reflect a high degree of competition based essentially on quality and innovation, rather than the normal competition based on quality, innovation, and price.

We find, therefore, that the exceptionally high rate of profit which generally marks the drug industry is not accompanied by any peculiar degree of risk, or by any unique difficulties in obtaining growth capital, and that industry profits have not been significantly reduced by new governmental regulations concerning drug safety, drug efficacy, or drug advertising.

It is also evident from this study that there are certain problem areas which call for cooperative study and action by the drug industry, private groups, and the Federal Government.

Accordingly, the Task Force recommends that the Secretary of Health, Education, and Welfare should call

one or more conferences with representatives of the drug industry, pharmacy, clinical medicine, and consumer groups to consider--

- (a) Provision of incentives to the drug industry to invest more research effort in products representing significant improvements to therapy and less in duplicative, noncontributory drug products and combinations.
- (b) Development of a registration and licensing system under which no drug product would be permitted in interstate commerce unless produced under quality control standards set by the Secretary of Health, Education, and Welfare.
- (c) Limitation of free drug samples to those specifically requested by prescribers, by industry agreement or legislation.
- (d) Development of more effective methods for ascertaining actual acquisition costs of prescription drugs.

Similarly, it is evident that certain other areas of concern require detailed analysis by appropriate agencies of the Federal Government.

The Task Force therefore recommends that the Secretary of Health, Education, and Welfare should call for a joint study by the Department of Health, Education, and Welfare, the Department of Commerce, the Department of Justice, the Federal Trade Commission, and other Federal agencies to consider--

- (a) The substantial differences in the prices at which drug products are offered to community pharmacies and to hospitals and government agencies.
- (b) The substantial differences in the prices at which drug products are offered to American and foreign purchasers.
- (c) Revision of patent and trademark laws on prescription drugs.

THE DRUG DISTRIBUTORS

Between the manufacturers who make drugs and the patients who purchase them is a large, complex distribution network.

Included in this network are the major drug vendors--independent pharmacies, chain drugstores, prescription pharmacies, mail order pharmacies, hospital pharmacies, dispensing physicians, and others. Considered with them in this section are the drug wholesalers.

Of the average prescription drug dollar paid by the consumer, about 50 cents is now taken by the manufacturer, 10 cents by the wholesaler, and 40 cents by the retailer.

During the past three decades, the operations of this system have undergone significant changes. For example, before World War II, most of all the drug products handled were in bulk form, and were compounded into tablets, capsules, powders, solutions or other dosage forms by the pharmacist. Now about 95 percent are furnished by the manufacturer in final dosage form, ready for consumption.

Formerly, wholesalers handled the overwhelming proportion of drug products. Now, with manufacturers tending to sell directly to hospitals and the larger independent pharmacies and chains, the wholesalers handle only about 48 percent of the dollar volume of the market.

In the years to come, other changes in the number and nature of both wholesale and retail outlets will undoubtedly occur as the result of continuing economic pressures, health manpower shortages, the expansion of new types of careers in pharmacy, and the introduction of innovations enabling drug distributors to respond more effectively and efficiently to the health needs of patients.

Prescription Price Information

There is an obvious need for patients to be able to determine readily the prices charged by the various pharmacies in their community. This appears to be particularly important in the case of long-term maintenance drugs.

The Task Force recognizes the difficulties in making such information easily available. Many patients are not told which drug has been prescribed for them--or are unable to decipher the physician's prescription. In many States,

laws or regulations forbid pharmacies to advertise; even without such rules, however, advertising current prices on many thousands of different drugs and dosage forms would pose formidable practical problems. Physicians, especially those in large cities, are likely to be unaware of the different prices which may be set at different pharmacies.

The Task Force also recognizes that the retail price of the prescription includes not only the cost of the ingredients, but also in some instances the availability of home delivery and 24-hour-a-day operations, as well as the professional services of the pharmacist--and that different pharmacists may wish to place different values on such services.

It recognizes that many or most patients may wish to select a pharmacy more on the basis of convenient location than on the basis of price.

Nevertheless, if the patient is to maintain the right to select a pharmacy, he also has a right to know the prices it charges and to compare these with other prices.

The Task Force finds there is a need for medical associations, pharmacy associations and consumer groups, working together at the local level, to develop mechanisms

whereby patients may obtain information on local prescription prices, especially for long-term maintenance drugs.

Prescription Label Information

It is frequently necessary for a physician to determine the nature and amount of a prescription drug which a patient has been taking. In some instances--as in the case of a suspected adverse drug reaction, or accidental or deliberate overdose--the rapid identification of a drug may be a matter of life and death.

As a step in improving the quality of health care, the Task Force recommends that the Congress should enact legislation requiring that the containers of all dispensed prescription drugs be labeled with the identity, strength and quantity of the product, except where this is waived upon specific orders of the prescribers.

To promote efficiency and minimize errors, the Task Force recommends that encouragement should be given to the wider use of prepackage dispensing, in which manufacturers prepare and pharmacists dispense tablets and capsules in precounted form, in sealed, prelabeled containers, and in such numbers as conform to those most frequently prescribed by physicians.

The New Role of Pharmacy

The pharmacy profession currently faces a dilemma which is partly though not entirely of its own making.

Many other aspects of health care--the practice of medicine and surgery, hospital operations, and particularly drug manufacture--have developed and adopted new devices and techniques which have remarkably improved the provision of health services. In contrast, the number of important new methods introduced to enhance the efficiency of retail pharmacy operations, at least during the past two or three decades, has not been noteworthy.

The Task Force recommends that the National Center for Health Services Research and Development should develop and support research to improve the efficiency and effectiveness of community and hospital pharmacy operations.

The role of the pharmacist is viewed by many people as simply transferring pills from a large bottle to a small one--counting tablets, typing labels, and calculating the price. Much of his time is seen as devoted to routine merchandising of cosmetics, shaving supplies, stationery and other commodities which have little or no relationship to health care.

This has raised doubts concerning the relevance of modern pharmacy education. As with other members of health professions, on the one hand, it would seem that much of the traditional education is not utilized, since a nonprofessional pharmacist--working under the supervision of a licensed pharmacist--can effectively perform many of the routine tasks of counting, labeling, and pricing. At the same time, many pharmacists are seeking a new role as a drug information specialist, and thus it would appear that their formal education has not taken this into account.

These problems regarding what the role of the pharmacist properly is--or should be--deserve careful consideration.

Pharmacist Aides

Experience in numerous pharmacies--military and non-military Federal installations, nongovernmental hospitals, and others--has demonstrated that individuals without formal pharmacy education can effectively undertake many of the routine activities of pharmacists, under the supervision of a licensed pharmacist.

Such activities offer the possibility of developing the career of pharmacist aide, comparable to the nursing aide, the orthopedic aide, the pediatric aide, the obstetrical aide, and similar paramedical positions.

Drug Information Specialists

At the other end of the spectrum, it is also becoming evident that appropriately trained pharmacists may become new and vital members of the total health team by serving as drug information specialists.

Some community pharmacists are already providing such services. They do not prescribe, but they discuss practical details of drug administration, possible side-effects, and other facets of drug use with each patient to whom a prescription drug is dispensed. They maintain patient or family records which contain data on drugs which have been dispensed to each patient, allergic responses, and adverse reactions. They call to the attention of the physician any prescriptions which may have been written for the same patient by other physicians, and they refer to him any prescriptions which may involve drug-interaction, synergism, or similar effects.

Some hospitals--especially teaching institutions and those in major medical center complexes--are already using pharmacists as consultants on drug therapy. They serve not only as drug distributors, but also as sources of drug data for physicians, interns, residents, and nurses. They may participate in ward rounds with the staff, providing valuable drug information on both old and new drug products. Although they do not prescribe for patients, they enable the physicians who do prescribe to keep up more effectively with drug information.

While some pharmacists are already serving as drug information specialists, and others are probably competent to do so, not all pharmacists have adequate competency in this field. Some licensed pharmacists have received five or even six years of formal college training, but about 15 percent of those now in practice have received two years or less of formal pharmacy education, and nearly half of these have had courses lasting only about six months.

Pharmacy Education

The manner in which pharmacists, pharmacy associations, pharmacy schools, and the pertinent State pharmacy agencies respond to increasing demands for pharmaceutical services will unquestionably determine in large measure how the

pharmacy profession will evolve during the years to come.

The Task Force commends the efforts of those pharmacy schools and State pharmacy associations which are already stressing continuing postgraduate education.

As a guide to the responses which should be made, there is a clear need for a broad study of pharmacy education similar to the famed Flexner study of medical education made half a century ago.

The Task Force therefore recommends that the Bureau of Health Manpower should support--

- (a) The development of a pharmacist aide curriculum in junior colleges and other educational institutions.
- (b) The development of appropriate curricula in medical and pharmacy schools for training pharmacists to serve as drug information specialists on the health team.
- (c) A broad study of present and future requirements in pharmacy, adequacy of current pharmacy education, and the educational changes which must be made.

Pharmacy Laws

The present patchwork of State pharmacy laws, regulations, and codes of ethics obviously reflects attempts to cope with a variety of pharmacy problems on a piecemeal basis. Whether they are aimed at the protection of the public health or the prevention of competition--fair or unfair--is not clear in all cases.

Many of these rules seem to have derived from periods of manpower excesses. They block efforts to cope with the present shortages of skilled manpower, the need for mobility to meet rapidly changing health needs, and the probable development of new careers in pharmacy.

The Task Force recommends that the Health Services and Mental Health Administration should support studies of State laws, regulations, and codes, with priority given to the establishment of model State licensing laws, uniform reciprocity standards, and provisions for the utilization of pharmacy aides.

THE DRUG PRESCRIBERS

In the modern use of drugs, important roles are played by the drug researcher, the manufacturer, the distributor, the pharmacist, and the official who carries the legal responsibility for drug safety, efficacy and quality. But the most strategic role is that of the physician who prescribes the drug.

It is the physician who has major responsibility for the welfare of the patient.

It is the physician who is constantly faced with an awesome assortment of competitive and often duplicative products.

It is the physician who is the target of a barrage of advice, information, guidance, and promotion from detail men, advertisements, medical articles, pamphlets, bulletins, and throw-away journals.

And it is the physician who--with or without adequate training and competent advice--must make the decision on which drug or drugs to prescribe.

On his decision may well depend the health or even the life of his patient. On it will depend, at least

in part, the quality, cost and effectiveness of any drug insurance program, governmental or nongovernmental. And on it will depend the economic well-being of a drug company.

Rational Prescribing

The appropriate selection of a drug--the right drug for the right patient, in the right amounts at the right times--is generally defined as rational prescribing, and any significant deviation is considered to be irrational prescribing.

Rational prescribing is obviously the result of judgments on many points--the safety and efficacy of the drug for the clinical problem at hand, the advantages or disadvantages of alternative forms of therapy, the most appropriate dosage form, the length and intensity of treatment, the possible side-effects or adverse reactions, and the possibility of drug interaction.

To these may be added judgments concerning relative costs.

Rational prescribing is clearly a major goal for the welfare of patients. It is likewise a major goal for any drug insurance program. Here, emphasis has been placed not directly on achieving rational prescribing but rather

on preventing some of the more serious or costly forms of irrational prescribing. Among the latter are these:

- The use of drugs without demonstrated efficacy.
- The use of drugs with an inherent hazard not justified by the seriousness of the illness.
- The use of drugs in excessive amounts, or for excessive periods of time, or inadequate amounts for inadequate periods.
- The use of a costly duplicative or "me-too" product when an equally effective but less expensive drug is available.
- The use of a costly combination product when equally effective but less expensive drugs are available individually.
- The simultaneous use of two or more drugs without appropriate consideration of their possible interaction.
- Multiple prescribing, by one or several physicians for the same patient, of drugs which may be unnecessary, cumulative, interacting, or needlessly expensive.

We find that some patients may be receiving as many as a dozen different drugs simultaneously, prescribed either by one or several different physicians, and that often physicians may not be aware that their patients are receiving drugs prescribed by others.

We find no reason to believe that any or all of these types of irrational prescribing can be effectively prevented--or that rational prescribing can be effectively induced--merely by rules and regulations. Instead, we believe the objective of rational prescribing can be reached most effectively through improving medical education--particularly in the area of clinical pharmacology--at both the undergraduate and postgraduate levels, supplying practicing physicians with objective data on which they can base their individual prescribing decisions, and supporting those in hospitals, clinics, medical societies and health insurance programs who are seeking to achieve rational prescribing by their fellow practitioners.

The Teaching of Pharmacology

In most American medical schools, the principal course in pharmacology is given during the second year. Generally, this is the only formal exposure of the student to the subject.

The nature of the pharmacology instruction has been a matter of much debate but little change. Although it is in reality a clinical as well as a basic science, it is taught primarily as a basic subject, with emphasis on the principles of drug action, a review of specific drug groups, examples of drug applications, and the broad fundamentals of prescription writing.

After the usual course in basic pharmacology, most medical students are given no formal training in the applied aspects of this field--in clinical pharmacology--but left to acquire what practical training they can absorb from a variety of courses in the several fields of clinical medicine.

Perhaps the most serious criticism of this informal exposure is that it fails to equip the soon-to-be physician with the essential scientific and critical attitudes towards the use of drugs and the evaluation of drug promotion--probably the most intensive promotion to which he

will be subjected for the rest of his professional career.

The Task Force has noted that some medical schools have responded to such a deficiency by establishing courses in clinical pharmacology or pharmacotherapeutics. In these courses dealing with the practical aspects of drug prescribing, emphasis is generally placed on such subjects as the design of comparative clinical drug trials, and the techniques of statistical analysis. Also included in some courses is the evaluation of drug advertising and promotional material, and the importance of drug costs.

Many who participate in these and related programs have received a major part of their training in the Section of Clinical Pharmacology in the National Heart Institute of the National Institutes of Health.

The Task Force recommends that the Department of Health, Education, and Welfare should provide expanded support to medical schools, enabling them to include a course in clinical pharmacology as an integral part of the medical curriculum.

Postgraduate Education

Upon entering private practice, the average physician, knowingly or unknowingly, becomes the key figure in drug marketing strategy.

- He must choose from a very large number of competitive and often duplicative products.
- He must deal with a very large amount of advice, biased or unbiased, from detail men, advertisements and other forms of promotion.
- Substantial efforts are made on his behalf by the drug industry and others to prevent any interference with his right to prescribe as he sees fit.
- Finally, it is assumed that he has the training, experience, and time to weigh the claims and available evidence, and thus to make the proper selection.

Everything, of course, hinges on the validity of this final assumption.

We find that few practicing physicians seem inclined to voice any question of their competency in this field. We have noted, however, that the ability of an individual

physician to make sound judgments under these quite confusing conditions is now a matter of serious concern to leading clinicians, scientists, and medical educators. A distinguished pharmacologist, for example, has stated that lack of knowledge and sophistication in the proper use of drugs is perhaps the greatest deficiency of the average physician today. Other medical leaders have pointed to the wide discrepancy in the prescribing habits of the average physician as compared to the prescribing methods recommended by panels of medical experts. Still others have commented on the continued use by the average physician of products which have been found unnecessary or unacceptable by specially qualified therapeutics committees in hospitals and clinics.

We note that the most widely used source of prescribing information is essentially a compilation of the most widely advertised drugs.

The responsibility for these and other deficiencies has been placed on various factors:

--Inadequate training in the clinical application of drug knowledge during the undergraduate medical curriculum.

- Inadequate sources of objective information on both drug properties and drug costs.
- Widespread reliance by prescribers for their continuing education upon the promotional materials distributed by drug manufacturers.
- The exceedingly rapid rate of introduction and obsolescence of prescription drug specialties.
- The limited time available to practicing physicians to examine, evaluate, and maintain currency with the claims for both old drugs and newly marketed products.
- The constant insistence on the idea that the average physician, without guidance from expert colleagues, does in fact possess the necessary ability to make scientifically sound judgments in this complicated field.

Information Sources

Several significant approaches have been attempted to cope with this problem. In the United States, a small number of independent publications--which do not publish advertising--seek to present objective evalua-

tions of the efficacy, safety, rationality, and occasionally the costs of specific drugs. These have relatively limited circulation, but are highly esteemed by medical leaders.

Many American hospitals and clinics utilize pharmacy and therapeutics committees to develop formularies which serve as guidelines to the staff members of the institutions. These, too, appear to contribute significantly to rational prescribing.

Other approaches to the problem of communicating objective and updated drug information have been proposed. These include, among others, closed-circuit television programs originating in medical centers; the development of community pharmacy and therapeutics committees; and the utilization of existing regional medical programs to sponsor continuing drug information programs; and the use of hospital pharmacies as drug information centers.

Several foreign drug programs--notably those in Great Britain, Australia, and New Zealand--provide all physicians with prescribing guidelines prepared by panels of independent medical experts. Such publications--frequently updated to meet changing conditions--have been widely accepted by the medical profession in those countries.

In consideration of these factors, in view of the unfilled informational needs evident in this country, and as a major contribution to improving the quality of health care, the Task Force recommends that the Department of Health, Education, and Welfare should establish or support a publication providing objective, up-to-date information and guidelines on drug therapy, based on the expert advice of the medical community.

We recommend that the Department of Health, Education, and Welfare should support the efforts of county medical societies, pharmacy and therapeutics committees, medical foundations, and medical schools in taking the responsibility for providing continuing education to physicians on rational prescribing.

The Bureau of Health Manpower, the Division of Regional Medical Programs, and the National Library of Medicine in particular should assign high priority to the support of such efforts.

Finally, we affirm our interim recommendation that the Secretary of Health, Education, and Welfare should be authorized to publish and distribute a drug compendium listing all lawfully available prescription drugs, including such information as available dosage forms, clinical effects, indications, and contraindications for use, and methods of administration, together with price information on each listed product.

DRUG QUALITY

During the past several years, the clinical equivalency of generic name products has been the center of particularly heated controversy.

This issue may be presented as follows:

--Given two drug products containing essentially the same amount of the same active ingredient--that is, two chemical equivalents--will they give essentially the same clinical effects?

This question, of increasing interest to both physicians and patients, is now under careful consideration by the scientific community. Objective research has shown that in certain instances the clinical effects may not be the same.

The Task Force has found, however, that lack of clinical equivalency among chemical equivalents meeting all official standards has been grossly exaggerated as a major hazard to the public health. Where low-cost chemical equivalents have been employed--in foreign drug programs, in leading American hospitals, in State welfare programs, in Veterans Administration and Public Health Service hospitals, and in American military operations--

instances of clinical nonequivalency have seldom been reported, and few of these have had significant therapeutic consequences.

Even though such cases are few, and others may well be reported in the future, these cannot be ignored, and the problem deserves careful consideration because of the medical and economic policies which are involved.

The interrelation of medical and economic factors is especially obvious in the case of two chemically equivalent products, both containing the same amount of the active ingredient and both meeting legal standards, but priced at different levels.

If the physician can be given reasonable assurance that two such competitive products will, in fact, give predictably equivalent clinical effects, then his choice between the two may well be based on relative costs. Under such conditions, there would be little justification for prescribing a relatively expensive brand of a drug when an equally effective counterpart is available at substantially lower cost. Similarly, there would be little justification for a Federal drug program to provide for reimbursement of such an expensive brand.

But if the physician cannot be given this assurance, his clinical judgment would dictate that he use only the product which can be expected to yield the desired clinical effects--regardless of cost or any other nonmedical factor.

The physician should be given assurance--not in the form of advertising, promotion, or the established image of the manufacturer involved, but in the form of objective, scientific data. In view of the thousands of drug products on the market, the accumulation of such data might seem to be monumental. But, with the exception of a few drugs for which adequate analytical methods are currently unknown, the Task Force has found that the problem is by no means insoluble.

Clinical Equivalency and Biological Equivalency

For the direct determination of clinical equivalency, it would be necessary to compare drug products containing the same active ingredient, in the same tablet or capsule or other dosage form, in the same amounts, and measurement of their relative effects in human patients in the alleviation of symptoms or the control of a specific disease.

Except perhaps in rare instances, such a comparison appears to be impractical at this time. It would be time consuming and costly. It would be complicated not only by individual human differences but by differences in the symptoms or diseases under consideration.

Clinical equivalency studies could be conducted in experimental animals, but the nature of specific diseases and the nature of drug absorption and action in animals and human beings may not be directly comparable in all cases.

Instead, attention has been directed to the use of biological equivalency--or relative biological or physiological availability--measured in normal subjects as a proxy for the direct measurement and comparison of therapeutic effects.

This is based on the general agreement among pharmacologists that with most drugs--certainly those taken orally for their effect on internal tissues and organs--their therapeutic effectiveness will be closely related to the absorption of the active ingredient into the blood stream.

Thus, it is assumed that if the active ingredient in two or more chemically equivalent products reaches the blood (or other fluid or tissue)--and becomes biologically or physiologically available--at the same time and in the same amounts, their therapeutic effects will be essentially the same.

Among the formulation factors which may be involved here, and involved in any possible nonequivalency of orally ingested products, are particle size; crystal form; the pressures and other conditions used in tablet-making; and adjuvants, such as substances incorporated as fillers, lubricants, binders, coatings, flavorings, colorings, and tablet-disintegrating agents.

Attention has also been directed toward physico-chemical tests which might be used to indicate biological equivalency--and, in turn, clinical equivalency. Perhaps the most important of these is the dissolution rate. Once a drug is dissolved in the gastrointestinal fluid, absorption is usually rapid. It is not surprising, therefore, that reported instances of clinical nonequivalency are rare among drugs which are highly soluble or administered in solution but most frequent among drugs

of inherently low solubility which are administered in solid dosage forms such as tablets and capsules.

Biological Equivalency Trials

In consideration of the foregoing, the Task Force initiated a program in the fall of 1967 to determine scientifically the biological equivalency of a number of chemical equivalents.

A major phase of the investigation was an attempt to determine whether any observed differences in biological equivalency could be related to differences in the physical or chemical characteristics of the products.

It was recognized at the outset that such trials were urgently needed for relatively few drugs. For example, among the 409 products most widely used by the elderly--and which accounted for about 88 percent of all prescription drugs dispensed to this group, there were only 89 which were dispensed under brand name but could have been dispensed under generic name from one or more additional suppliers. An additional 30 were actually dispensed under generic name.

Among these, the priority for clinical trials was determined on the basis of the following criteria:

1. The product is generally considered as a "critical" drug--that is, required for the control of a disease, rather than for the alleviation of temporary symptoms.
2. It is generally dispensed in solid form--as a tablet or capsule.
3. The active ingredient is relatively insoluble.
4. Particular attention should be given to those drugs which had previously been the subject of reported or suspected nonequivalency or therapeutic failure.

A number of drugs meeting these criteria were selected by the Task Force in consultation with representatives of clinical medicine, pharmacology, pharmacy, brand name and generic name manufacturers, the Food and Drug Administration, and other governmental agencies. Biological equivalency studies on these products in human volunteers began late in 1967 in the FDA laboratories; at Georgetown University, under an FDA contract; and at the Public Health Service Hospital in San Francisco.

(Detailed results of these investigations are not presented in this report. Since they obviously may be of practical concern to physicians and scientists, the data are being announced as quickly as they become available in the usual medical and technical publications.)

As an important part of these trials, attempts were made to determine whether any observed differences in biological availability could be correlated with differences in any physico-chemical characteristics of the product. Such physico-chemical differences could presumably be utilized in developing new and approved specifications for drug quality testing.

Although complete data are not available, it appears noteworthy that all instances of biological nonequivalency found in the first phases of the trials were, in fact, marked by differences in dissolution rate.

The Task Force recommends that the present clinical trials to determine the biological equivalency of important chemical equivalents should be continued by the Department of Health, Education, and Welfare on a high priority basis.

Drug Standards

In the United States, the two most important official compendia of drug standards and specifications are the U.S. Pharmacopeia (USP) and the National Formulary (NF). Both have long and distinguished histories, and are highly regarded by physicians and scientists.

Although both publications have clearly stated that they cannot guarantee it, their standards and specifications have been widely presumed to assure the clinical equivalency of chemical equivalents.

The recent finding that some chemical equivalents are not biologically equivalent, even though they conform to existing USP and NF standards, has shown that certain of these standards may require revision.

During the past year, representatives of both USP and NF have been cooperating closely with the Task Force to meet this challenge. It is expected that existing specifications will be tightened where indicated and possible, and that these modifications will be incorporated in the revised USP and NF editions now in preparation.

The Task Force commends the U.S. Pharmacopeia and the National Formulary for their prompt and responsible approach to the problem of clinical equivalency.

Quality Control

The establishment and enforcement of product standards and specifications represents one important approach to the problem of drug quality and clinical equivalency.

Another is the establishment and rigid enforcement of appropriate quality control standards in all aspects of drug production and packaging. The Task Force has already recommended that a registration and licensing system be considered under which drug producers and packagers would be required to conform to a code of Good Manufacturing Practices and other criteria. (See Page 48)

We likewise recommend that adequate financial support should be provided to the Food and Drug Administration for necessary educational and inspection operations so that acceptable quality control methods can be instituted and properly maintained in all drug manufacturing and packaging establishments.

We recommend that the Food and Drug Administration should be authorized to provide additional support, including grants-in-aid, to State and local agencies in order to improve quality control of prescription drugs in intrastate commerce.

The enforcement of an acceptable quality control program may be expected to have these effects:

- Many reputable manufacturers, both large and small, already maintain acceptable quality control programs, and will merely be obliged to continue them.
- Some manufacturers may elect not to institute such programs, and their products would therefore be found unacceptable for shipment in interstate commerce.
- Other manufacturers will elect to institute and maintain acceptable quality control methods. This may result in slightly higher production costs, which the manufacturers would most probably cover by setting slightly higher prices on their products.

The Task Force is strongly convinced that the added investment of Federal funds to require acceptable quality

control methods, and the slightly higher drug prices that may result in some instances, would be more than justified by the improvement in drug quality that would be achieved.

We have given careful consideration to proposals for the placement of fulltime Food and Drug Administration inspectors in every drug manufacturing plant--large and small--but believe this would involve unjustifiably heavy expenses and inappropriate use of skilled manpower.

We have also considered proposals for the extension of batch certification--now applied mainly for insulin, antibiotics and biologicals--to all drugs, requiring FDA testing and approval at the manufacturer's expense before any batch may be released for distribution. We feel this would place an unnecessarily heavy and costly burden on manufacturers which would be reflected in unnecessarily higher prices to consumers.

Instead, we find that further study is needed on the use of self-certification, with each manufacturer instituting and maintaining a quality certifying program approved by FDA.

ONGOING PROGRAMS

The provision of out-of-hospital prescription drugs through governmental or private insurance programs has been undertaken in one form or another for nearly a century. Many of these include techniques and approaches which deserve consideration in any out-of-hospital program that might be designed under Medicare.

Accordingly, the Task Force has examined a wide variety of ongoing programs--all of the major drug programs conducted by the Federal Government, a number of selected State programs, six of the leading private programs in this country, and the major programs in eleven foreign countries.

These programs are not directly comparable. In some foreign countries, for example, national economic and social structures lend themselves to controls and methods of operation which are probably not suitable in the United States. Certain aspects of military drug programs may not be adaptable for civilian programs. Other approaches utilized in private programs may be impractical for a government operation.

Nevertheless, a study of these diverse systems has proved to be illuminating. It has clearly indicated

that out-of-hospital prescription drugs can be provided under programs that are medically acceptable and economically sound.

Federal Programs

Through direct purchase or reimbursement, the Federal Government is now concerned with the provision of prescription drugs through several major programs. As shown in Table 1, expenditures for drugs in these programs totaled more than \$491 million in fiscal year 1967.

DOD Military Procurement. The largest direct drug procurement program is that of the Department of Defense, with its responsibility for supplying about 3,000 military establishments in this country and overseas.

A major characteristic of the DOD operation is its testing and inspection program to assure drug quality and the ability of the products to withstand prolonged exposure to climatic extremes. DOD sets its own drug specifications, maintains its own manufacturing plant inspectors, and operates its own testing program. Manufacturers must undergo stringent pre-award surveys of their facilities as well as testing of their products

Table 1

ESTIMATED FEDERAL EXPENDITURES FOR
PRESCRIPTION DRUGS
(Fiscal Year 1967)

Direct Purchase	(million)
Department of Defense	\$ 111.0 <u>a/</u>
Public Health Service	4.1 <u>b/</u>
Veterans Administration	39.5 <u>c/</u>
Federal Supply Schedule Contracts	6.2 <u>d/</u>
Total Direct	<u>\$ 160.8</u>
Reimbursement Programs	
CHAMPUS	\$ 0.2
VA Hometown Pharmacies	2.9
Public Health Service	0.7
Medicare In-Hospital	230.0 <u>e/</u>
Medicaid	96.5 <u>f/</u>
Total Reimbursement	<u>\$ 330.3</u>
Total all Federal Drug Expenditures	\$ 491.1

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- a/ Includes \$92.4 million purchased through Defense Supply Center Philadelphia, Pa. and approximately \$15.7 million purchased through Federal Supply Schedule Contracts; remainder purchased locally.
- b/ Includes \$1.3 million purchased through PHS Supply Service Center, Perry Point, Md., and \$2.8 million from other sources including the Veterans Administration.
- c/ Includes \$14.6 million purchased through Federal Supply Schedule contracts administered by VA for General Services Administration.
- d/ Includes purchases for miscellaneous Federal agencies.
- e/ Includes \$115.0 million for overhead drug expenses of hospitals and extended care facilities.
- f/ Includes other Federally-supported State Public Assistance Programs; excludes \$85.5 million, which was the State portion of the total drug program expenses.

in DOD laboratories. After drug contracts are awarded, both the plant facilities and the stored products are continuously spot-checked, and DOD actively solicits reports from military hospitals and physicians on drug quality, therapeutic efficacy, and adverse reactions.

About 240 of the 1,200 drugs currently stocked are purchased under generic name.

The DOD policy is to purchase drugs under contract from the lowest "responsible bidder." It may buy foreign-made drugs where the acquisition cost is at least 50 percent less than "responsible" domestic bids. The same pre-award standards and continuing surveillance imposed on domestic firms are applied to foreign manufacturers with DOD contracts.

As a Federal purchasing agency, DOD may purchase patented products from unlicensed manufacturers.

DOD Military Medicare. Through its Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), the Department of Defense provides out-of-hospital prescription drugs through hometown pharmacies to some 6.5 million eligible retired military personnel and military dependents. Various carriers are used for program administration.

Any pharmacy willing to meet CHAMPUS requirements may participate. The pharmacist is reimbursed for the acquisition cost of the drug plus a dispensing fee which has been set for each State.

Each eligible beneficiary must first meet a deductible requirement of \$50 per year--or \$100 per year per family--and pay a co-insurance charge of 20 or 25 percent, depending on beneficiary status.

No formulary requirements are involved.

The average prescription price in 1967 was reported to be about \$4.15.

Veterans Administration. In 1967, the VA purchased drugs and biologicals costing \$39.5 million for use in its own hospitals and pharmacies, and also procured drugs for other Federal agencies, such as the Public Health Service and the Office of Economic Opportunity.

Of the drugs used in VA pharmacies, about 86 percent are purchased from some 250 manufacturers who have been approved by on-site inspections. Each VA hospital has its own drug formulary of about 700 to 2,000 items developed by its own pharmacy and therapeutics committee, and tailored to fit the needs of the institution. The

formularies are used as guidelines rather than prescribing limitations, since non-formulary drugs may also be prescribed.

Chemical equivalent drugs are widely used where available.

In addition, the VA Hometown Pharmacy Program provides out-of-hospital prescription drugs to eligible beneficiaries, generally those with service-connected disabilities. The hometown program, which involved an expenditure of \$2.7 million in 1967, provides for reimbursement to pharmacies on the basis of acquisition cost plus a dispensing fee. No formulary is used in this program, and no deductible or co-payment is required.

Office of Economic Opportunity. Through its Neighborhood Health Centers, OEO provides pharmaceutical services for about 800,000 persons in 44 programs.

Eligibility requirements vary but generally are based on a "poverty line" schedule, on Medicaid standards, or on other guidelines established by the community. Each center makes its own determination about the use of a formulary. No deductible or co-payment is required.

Several of the centers provide direct drug services in their own pharmacies, while the others provide for

reimbursement to community pharmacies on the basis of acquisition cost plus a dispensing fee.

Public Health Service. In 1967, PHS expended more than \$4 million for drugs for its own operations, and also purchased drugs for Civil Defense stockpiling.

Of the drugs procured for PHS activities, some were used by the National Institutes of Health and the National Institute of Mental Health, but most were dispensed through the Division of Direct Health Services--with 11 hospital and 14 clinic pharmacies--and the Division of Indian Health. The latter operates 51 hospitals with pharmacies, and contracts with about 200 community pharmacies that furnish prescription drugs to Indian beneficiaries.

Each PHS hospital has its own formulary, but exceptions are made for the provision of nonformulary drugs. Physicians who contract with PHS are not obliged to use the formularies.

Pharmacies participating under contract with the Division of Indian Health are required to dispense the least expensive drug products they have in stock which will meet the physician's requirements when a generic

prescription is written. The price may not exceed the price to the general public.

No deductibles or co-insurance requirements are involved in any of the PHS out-of-hospital programs.

Medicare. Data from the Medicare program relating to the cost of drugs provided to beneficiaries in hospitals and extended care facilities are not yet available. However, on the basis of recent studies of drug use in hospitals in general, it is estimated that in fiscal 1967 roughly \$230 million was spent under Medicare for drugs, with about half of this amount representing product cost and the remainder the cost of dispensing and administration. (See Table 1)

Under Medicare, in-hospital drugs must be listed in one of several official compendia or in a formulary established by the hospital's pharmacy and therapeutics committee. Medicare requires that drug charges to the government must be "reasonable."

Public Assistance. Under Medicaid and other public assistance programs with joint Federal-State support, an estimated \$182 million was spent for prescription drugs in fiscal year 1967, of which an estimated \$96.5 million was paid by the Federal Government, (Table 1). Federal-

State vendor payments of \$182 million represented 7.8 percent of all medical care services provided in that year, and were made to hospitals, pharmacists, and other licensed vendors.

The Federal share of payments to vendors for drugs and drug services ranged from 50 to 83 percent, depending on the nature and extent of the program in each State, with an average of about 53 percent.

In such programs, no deductibles or co-payments are generally involved, although one non-Medicaid State program included a co-payment requirement but provided funds to the recipients to cover such payments.

Further details on these public assistance programs are presented in the following section.

State Programs

Vendor drug programs for recipients of Medicaid and other public assistance funds are now operating in 38 States and Territories. The range in their utilization, costs, and benefits is very large.

Thus, among all eligible beneficiaries, the utilization rates in 1967 ranged from 26 percent in Missouri and Tennessee to 91 percent in New Hampshire and 99 percent in Rhode Island.

The average annual number of prescriptions per user ranged from about 10 in New Mexico to 46 in Indiana.

The average annual expenditure per user ranged from \$39.35 in New Jersey to \$148.95 in Florida, \$155.67 in Nebraska, and \$158.58 in Indiana.

The average cost per prescription ranged from \$2.91 in Kentucky and \$2.94 in Illinois to \$4.74 in New Mexico.

Because of the diversity and complexity of the various State drug programs, the Task Force selected five for intensive study--California, because of its size; Louisiana and West Virginia, because of their approach in approving drugs used only for the treatment of specific diseases; Kentucky, because of its limited formulary; and Pennsylvania, because of its extensive formulary, which is used primarily as a guide to prescribing.

Other studies were conducted on the programs in Indiana, Nebraska, North Carolina, Oklahoma, and South Dakota.

In nearly all of these States, per capita drug costs and average prescription prices for program beneficiaries were higher than those for the total public. Whether this was the result of program abuse or of the

greater health needs of those receiving public assistance cannot be readily determined.

There was no consistent pattern of vendor payment, with some States reimbursing on the basis of customary and usual charges, some on acquisition cost plus a percentage markup, some on acquisition cost plus a dispensing fee, and some using a combination of percentage markup plus dispensing fee. Several set dollar limits. There was no clearcut relationship between any of these methods and program costs.

Where acquisition cost was a factor in the reimbursing formula, this was generally presumed to be the listed wholesale price, although it is understood that this list price has little if any relationship to the actual acquisition cost. Few States made any efforts through spot audits to determine actual acquisition cost.

Administrative expenses have been estimated to average about 50 cents per prescription, with the lowest cost--about 20 cents--reported in Louisiana. Differences in estimating administrative costs, however, make it impossible to make exact comparisons.

Among the States studied, none was applying data processing techniques to the extent necessary for effective utilization review.

Only one State--North Carolina--had tested the effect of a deterrent charge to the patient. In February 1967, North Carolina required the recipient to pay the first dollar of the cost of each prescription, and at the same time provided beneficiaries with monthly cash payments from which to pay medical expenses. Within about two months, although the number of prescriptions actually increased, the total cost of the prescription drug program was reduced.

While there seemed to be wide agreement among officials of many States that such a co-payment requirement would probably be a highly effective method of cost control, there was no such agreement on the effect of this technique in limiting the access of welfare beneficiaries to the health care they required.

The influence of limited formularies alone also appears to be questionable. Although the use of a highly restrictive formulary is associated in several States with effective cost control, such control also has been noted in Pennsylvania, with a virtually unlimited

formulary but with restrictions on quantity and number of refills.

Many States urged or required the dispensing of low-cost chemical equivalent products where available. Under such conditions, no significant instances of lack of clinical equivalency were reported.

We find, therefore, that in Medicaid and other State public assistance programs, no single method will by itself guarantee program efficiency, but without at least two features--reasonable formulary restrictions and effective data processing procedures--program controls will be ineffective. Although a co-payment requirement may not be widely acceptable in public assistance drug programs, its value in controlling costs in other programs seems evident.

Private Programs

Several nongovernmental programs to provide prescription drugs to members of unions and other groups have been in operation in this country for many decades, and others have been developed in more recent years.

For special examination, the Task Force selected six of these--Prepaid Prescription Plans, Inc.; Paid Prescriptions, Inc.; United Mine Workers; the Kaiser

Foundation Health Plan; Group Health Cooperative of Puget Sound; and the new Blue Cross plan.

As in the case of State programs, these private programs offered a variety of approaches. Some utilized their own pharmacies, and some used community pharmacies. Several used restrictive formularies, while others reimbursed for any prescribed product.

All were financed through monthly dues or premiums.

Major economies in these private plans were found associated with the use of formularies, frequent field audits to determine actual acquisition costs by vendors, and the use of a co-payment or similar requirement. The greatest economies were noted in those programs in which the institution served as the purchaser of the drug products, rather than as a reimbursor, and thus could obtain competitive or negotiated bids.

Several of the programs included in this study either urged or required the use of available low-cost chemical equivalents. No significant problems with lack of clinical equivalency were reported.

Foreign Programs

The greatest experience with prescription drug programs has been achieved in a number of foreign countries.

Fifteen of them in eleven nations were selected by the Task Force for special study--Australia, Belgium, Denmark, France, Great Britain, The Netherlands, New Zealand, Norway, Sweden, West Germany, and the provincial programs of Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan in Canada. Less intensive studies were conducted on the programs in Italy and Switzerland.

All of these nations show wide variations in demographic characteristics, government operations, industrial development, social philosophy, local tradition, and even medical tradition, and certain portions of their health insurance programs may not be suitable for use in the United States. Nevertheless, most of the procedures considered for prescription drug insurance programs in this country have already been tried in one form or another in these foreign programs.

In all of the countries included in the Task Force study--which represent nearly all of the major prescription drug programs in the world--the program is financed by employee or employer contributions, or by voluntary or compulsory participation in various "sickness funds" and insurance plans.

Some, including several of the Canadian programs, are designed exclusively for public assistance beneficiaries. Others cover the entire population, regardless of economic status, while still others have programs providing one set of benefits to welfare beneficiaries or pensioners, and another set to those who are not public assistance recipients.

Most of the prescription drug programs, especially in Europe, are integral parts of national health insurance systems.

In most countries for which statistical data are available, it is evident that there has been a steady increase in the average number of prescriptions per year, in the average prescription cost, and in the cost of the entire program. Except in Canada, the prices of specific drug products and of average prescriptions are generally lower than those in the United States; these differences appear to reflect lower labor costs, lower purchasing power, and similar factors, and also more intense price competition among drug manufacturers.

In nearly all countries surveyed in this study, a formulary of one type or another is used to improve rational prescribing, ensure drug quality, and control

costs. In most, but not all cases, there are provisions for prescribing an unlisted drug when this is clinically indicated.

The drug lists of Norway, Sweden and Denmark are structured to provide only essential drugs for serious diseases. In France, Great Britain and West Germany, formularies are essentially unlimited, and in the last two countries are noncompulsory; all three of these countries, however, are currently considering the use of more restrictive formularies.

In Australia and New Zealand, and in several European countries, formularies have proved to be highly effective in controlling costs. The Australian government, for example, has no authority to set prices for drugs but uses inclusion in the formulary as an indirect means of price control--that is, if the price is considered too high in relation to its therapeutic advantages by a committee of medical advisors, a drug may not be included in the list. New Zealand negotiates prices, but will pay only at the level established for an acceptable chemical equivalent where one is available. Most of the countries have either established maximum retail prices or negotiated price agreements with manufacturers.

Compulsory licensing of patents is provided by law in most of the countries, but the law is seldom invoked. It may be used if the manufacturer of an "essential" or "necessary" drug refuses to reduce its price to what the health program considers to be a reasonable level.

With the exception of France, all countries in this group reimburse the drug vendor rather than the patient. The price paid to the vendor is usually determined on the basis of acquisition cost plus an established percentage markup, a dispensing fee, a container fee, or a combination of any of these. In The Netherlands, a capitation system is used in which the patient is required to have his prescription filled at a single pharmacy, and the pharmacist is paid a per capita fee for each patient registered with him.

In several countries, drug utilization review is provided through central or local boards or committees of physicians. In New Zealand, for example, medical representatives visit physicians to discuss drugs, local prescribing patterns and any individual prescribing habits which might seem to represent irrational prescribing. In Australia and Great Britain, these visits occur

when the individual physician's prescribing pattern appears to represent unusually high costs.

Nearly all of these countries recommend or require the use of low-cost chemical equivalents where available. No significant problems with lack of clinical equivalency have been reported. Controversy over generic name prescribing in Australia, New Zealand and most of the European countries studied by the Task Force has not reached the heights noted in the United States.

Quality control in many of the countries is achieved by registration of all drugs sold in the country, as well as by various types of drug testing. Often a drug evaluation committee or commission composed of physicians, pharmacists, and drug industry representatives has the responsibility for determining which drugs will be registered and which tests will be imposed. Testing varies from batch analysis to complete laboratory research of the formulation and its possible side effects.

Some programs call for patient participation through a fixed co-payment or percentage co-insurance. The effect of such a requirement was demonstrated in

Great Britain, when the co-payment requirement was abolished and program costs promptly rose substantially.

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From its consideration of ongoing prescription drug programs, the Task Force finds that a permanent mechanism is needed at the Federal level to collect, analyze and exchange information, and to provide effective coordination of drug-related activities among the agencies involved.

We therefore recommend that the Federal Interdepartmental Health Policy Council should concern itself with the coordination of all ongoing Federal prescription drug purchase and reimbursement programs.

We recommend that a special subcommittee of the Council should be appointed for this purpose.

DRUG CLASSIFICATION AND CODING

Within a few years, it may be expected that prescription drug benefits under existing public and private programs will involve several hundred million prescriptions annually.

Without a universal coding, classification and identification system--a common language for communicating essential information--the administrative and accounting costs for processing such a volume will inflate program costs beyond acceptable limits.

To find methods of coping with this problem, the Task Force appointed ad hoc committees of experts on classification and coding which began a series of meetings in July 1967. In these conferences, criteria were established for a system under which all known pharmaceutical preparations could be identified and desired data stored and retrieved by use of existing and planned electronic data processing techniques and equipment.

Classification

By July 1968, the proposed classification system was in final draft. It is the result of the joint efforts of representatives of the American Medical Association, the

U.S. Pharmacopeia, the National Formulary, the American Society of Hospital Pharmacists, the Drug Information Association, the National Pharmaceutical Council, the Pharmaceutical Manufacturers Association, the Food and Drug Administration, the National Library of Medicine, and various universities and State agencies.

Based on the vital necessity to relate cost analysis and utilization studies to how and why drugs are being used, the classification scheme is designed to accomodate products by categories reflecting their intended therapeutic action. This version makes it possible to place drugs in multiple settings. Final data collection will survey these settings and provide cost breakdowns and other cost analyses according to actual drug usage.

Application of the classification will have obvious importance for economic administrative procedures. More significantly, it will play an important part in developing information needed for improving the quality of health care.

The Task Force recommends that the Department of Health, Education, and Welfare, the Department of Defense, and the Veterans Administration should test the proposed

drug classification system to determine the feasibility of its eventual use in all public and private drug programs.

We commend those whose efforts made possible the development of the system.

Drug Coding

In the different aspects of drug manufacturing, distribution, sales, use, utilization review, accounting, cost analysis, and other marketing or administrative procedures, many different kinds of information may be needed. Basic to all of them, however, is information which will identify (a) the manufacturer, (b) the product, dosage form and strength, and (c) the package size, and which also is in a form which can be transmitted, stored and retrieved through electronic data processing systems.

Logically, the identification number would be assigned for all drugs on the market, and for any new drug at the time the New Drug Application is approved.

The number should be part of the required labeling, and ideally could be used to identify each individual tablet or capsule by printing techniques which are already being used by some drug manufacturers.

In addition, the number should be utilized in the coding for a proposed international adverse drug reaction reporting system which is now under consideration.

As a result of Task Force studies, it appears that an appropriate code can be developed by the use of a nine-character identification system utilizing both letters and numbers. The first three numbers would identify the labeler of the product (in most cases the labeler would also be the manufacturer), the next four would identify the drug, dosage form and strength, and the last two would identify the package size.

It is believed that such an identifying system would be able to accomodate a virtually unlimited number of different drug products.

• The Task Force recommends that--

- (a) An appropriate identifying code number should be made part of all drug labels, package inserts, catalogs and advertising;
- (b) An appropriate coding system should be developed and tested by government and industry for this purpose;

- (c) After consideration of the results of this test, appropriate legislation should be introduced to require coding of all drug products in interstate commerce.

We commend those whose efforts are making the development of a new coding system possible.

As part of its activities in this field, the Task Force also supported development of an experimental National Drug Code Directory, prepared in preliminary form by the Food and Drug Administration to serve as a directory of essentially all prescription and over-the-counter drugs.

We recommend that the drug code adopted by government and industry be utilized in the National Drug Code Directory.

UTILIZATION REVIEW

In any drug program, utilization review is a dynamic process aimed first at rational prescribing and the consequent improvement of the quality of health care, and second at minimizing needless expenditures.

In many hospitals, staff committees of experts have long taken the responsibility of reviewing the records of their fellow physicians and offering such advice or taking such disciplinary action as they deemed necessary. During the past two years, utilization review programs have been instituted to improve the quality of medical care under the hospital program of Medicare. Similar reviews are used in several American and foreign drug programs to improve the quality of drug prescribing.

It should be the responsibility of a program administration to institute a drug utilization review, and provide the necessary data and whatever statistical analysis may be required.

But the implementation--the establishment and improvement of guidelines, the provision for acceptable deviations, the limitation of irrational prescribing, the prevention of fraudulent practices, and other professional judgments--

should be mainly the responsibility of clinicians, pharmacologists, and pharmacists who are widely respected as objective, well-informed, and appreciative of the needs of both physicians and patients, and who would work with their colleagues at the State or local level.

There is an evident need for further research to develop and test various approaches to effective utilization review--approaches which would be most acceptable to physicians, pharmacists, consumers and others, and which would obtain their effective support.

The Task Force therefore recommends that the National Center for Health Services Research and Development, in cooperation with State and local medical groups, community pharmacies, hospitals, and consumer groups, should support pilot research projects on prescription drug utilization review methods.

(Whereupon, at 12:05 p.m., the subcommittee adjourned subject to the call of the Chair.)

APPENDICES

APPENDIX I

CORRESPONDENCE FROM DR. ROBERT E. HOWARD, PRESIDENT, OHIO STATE MEDICAL ASSOCIATION, TO SENATOR NELSON, DATED OCTOBER 18, 1967, RE DRUGS

OHIO STATE MEDICAL ASSOCIATION,
Cincinnati, Ohio, October 18, 1967.

Senator GAYLORD NELSON,
Chairman, Subcommittee on Monopoly,
Senate Select Committee on Small Business,
Washington, D.C.

DEAR SENATOR NELSON: The Ohio State Medical Association is taking this means of submitting its views on certain matters of pressing concern to the medical profession which have emerged during the current investigation of the drug industry by the Monopoly Subcommittee of the Senate Small Business Committee. The Association is composed of more than 10,000 practicing physicians representing all 88 counties throughout Ohio.

We respectfully ask that this statement be included in the published record of the hearings.

Much has been said during the investigation regarding "generic equivalency" in the drug field. Our deep and most sincere apprehensions have been aroused by reports of the testimony which have been widely published in the press and broadcast over the air.

We note that some witnesses have stated categorically, and others have implied, that there is little or no difference in the therapeutic effectiveness of drugs bearing the same generic name; that, if they meet the minimum standards of the U.S. Pharmacopoeia or the National Formulary, their manufacturing source does not matter. Further, it has become plain that the testimony has been weighted as to associate wrongfully the word "generic" with the word "cheaper" in its connotation to the public.

The result of this has been to promote the fallacious and dangerous belief that generic prescribing is not only safe from a medical viewpoint but is a desirable way for the physician to save the patient money in the purchase of his medicines. The particular rationale in this instance is that generic prescribing is a reasonable way for the government to hold down the cost of the health care it finances. Certainly, the saving of tax funds is a laudable aim and, in this frame of reference, the generic prescribing proposal can be expected to have broad popular appeal.

Nor can the patient be blamed if he is enticed by the promise of just as good drug products for less money. Like everybody else, he wants a bargain when he can get one. Lacking scientific knowledge and understanding of the many complexities involved in this matter, neither the taxpayer nor the patient can help but be swayed by arguments which carry the authority and prestige of a Congressional committee.

We have not seen produced any scientific data or substantive expert testimony which has been offered the Subcommittee to support the claim of generic equivalency of drugs. Indeed, we are certain that such evidence has not been placed before you because we know it does not exist. A comprehensive study of this question, so basic to your entire inquiry, is now being made by the Department of Health, Education and Welfare at the direction of the President. When it is completed, we feel confident it will illuminate the fallacy of so-called "generic equivalent." We urge you to withhold until then judgment on the testimony, the sweeping claims, the unsupported generalizations you have heard over the past several months; for, without incontrovertible scientific evidence, this controversy cannot be resolved by the public or members of Congress.

On the general question of drug costs, we would first point out that this is by far the smallest portion of the health care bill and it has declined in recent years, both as to the prices of the drugs themselves and the proportion they represent of the total costs of an illness. Prescription drugs now account for only 9.8¢ of the health care dollar, according to the Department of Commerce, compared with 11.7¢ a decade ago.

The Department of Labor reported in September that the price of prescription drugs on its Consumer Price Index has dropped 11.2% since the 1957-59 base period. We believe these trends, registered in a period when the prices of virtually all other commodities have been going up, raise serious questions as to the validity of the argument over drug costs as a pretext for requiring generic prescribing for any segment of the population, especially when such a program is advanced as a government economy measure.

We are in complete accord with the position taken by the American Medical Association on several occasions that physicians should supplement their medical judgment with cost considerations when prescribing for their patients. But this cannot mean that price is to be established as the paramount consideration in the selection of a medicine, over safety, and effectiveness. As physicians, we are professionally and ethically concerned that our patients receive only the highest quality products made by manufacturers who value highly their names and reputations and are known to, and trusted by, the prescribers.

The pressure for economy in prescriptions, as in many consumerist arguments, makes use only of the fact that fit a tendentious hypothesis. It is indeed a fact that some medications are available at a lower cost in identical form without a brand name. It is also a fact that, to some patients, it would make little, if any, difference what brand of a particular medication were prescribed. In these instances, the physician may wish to specify the least costly variety, provided quality is not sacrificed.

But the minor advantages of prescribing generic drugs stop at that point and the disadvantages begin. Health care personnel, knowledgeable in pharmaceutical manufacture and dispensing, are fully aware of the dangers of using non-brand-name drugs. And this danger does exist. We know of no hospital that requires generic prescribing of its staff members, including military hospitals about which so much has been said before the Subcommittee.

One of our professional colleagues, Doctor Durward Hall, Congressman from Missouri, has informed you of the rigid standards enforced by the military in the procurement of drugs, and the meticulous care exercised to assure the purchase of only quality products. We assume it has been established to the Subcommittee's satisfaction that the formularies of military hospitals are stocked with products of proven quality. Even beyond this, there is not a physician practicing in one of those institutions who does not possess complete discretion to prescribe precisely the medicine he deems best for a particular patient. His peers have not limited him to the formulary, stocked as it may be with products obtained under the most stringent requirements. If the medicine he prescribes is not on the shelves it will be specially purchased.

There must be a reason for this. There is. It lies at the heart of the generic prescribing issue.

From the physician's point of view, brand name drugs often have important and vital properties, in addition to the active chemical ingredients, that make them especially valuable in the treatment of certain patients. The carefully controlled and precisely stated characteristics of the drug are significant information that the prescribing physician relies on when he specifies the drug for his patient. The patient's response to a prescribed drug can be scientifically evaluated because the physician knows exactly what it was that he prescribed. If the doctor is forced to prescribe a generic drug, he may lose an important element of control over the treatment of his patient.

Where there are successive refills for long term treatment, the physician would again be deprived of control over his patient's treatment unless each new supply had the same variables—coating, solubility, disintegration time, base, etc. We submit that this is impossible when the medicine comes from several different manufacturers with different methods and standards of quality control. Under these conditions, there could be variations in therapeutic response which might mislead the physician in his diagnosis or alter the patient's progress. This hazard can be avoided if each refill comes from the same manufacturer who is known and trusted by the prescribing physician.

Interestingly, there is nothing at the present time that prevents physicians from prescribing generically. We believe most of our colleagues do in cases compatible with the patient's needs. But when we prescribe, for example, Dicumarol, an anti-coagulant, the dose and the therapeutic action must be precise and reliable. Too much means internal bleeding; too little means clotting. In either instance, the result could be fatal. And once the proper dosage has been established for the individual, it must remain constant. It could be altered by a change from the product of one manufacturer to that of another, thereby causing a dangerous reaction in the patient.

There is no other way to express it. Professionally and ethically—for the good of the patient—we cannot but be seriously alarmed by the possibility that we may be confronted with the unscientific requirement that we prescribe generically for our patients without knowing anything about the medicine that will be dispensed, its pharmacological components, actions and reactions and what manufacturer stands behind it.

Chances cannot be taken with any medicine; they simply cannot be taken in the area of critical drugs. When we prescribe digitalis or nitroglycerin for our heart patients, we must know what we can expect the medicine to do, and our experience with the same product in the past tells us that. We cannot know if the medicine is from an indeterminate or questionable source which may change each time the prescription is refilled. The range between a toxic dose and a therapeutic dose is too narrow to allow room for the slightest doubt about these drug products to exist in the physician's mind.

We previously mentioned Dr. Hall's testimony before this Subcommittee. You will recall that he dealt with the high proportion of rejections of both drug manufacturing plants and drug products by military procurement officers as a result of their analysis and inspection procedures. The facts which he provided, we believe, constitute a devastating refutation of the arguments for generic prescribing, whether enforced by direct or indirect means.

Obviously, there were drugs offered to the government which were not manufactured under effective and exacting quality control methods. There were plants seeking to do business with the government which were found wanting for sanitary or other important reasons.

There are no assurances that the same drugs are not being sold to the public at the present time, or that the rejected plants are not on the market with products of dubious effectiveness. These could be the "inexpensive" generic drugs, the dangerous drugs, which would be dispensed under prescriptions failing to identify the manufacturer of the product desired by the physician or to specify it by brand name.

Proposals are now pending in Congress for the establishment of a national drug formulary from which prescribing physicians would be required to select medicines in order for their patients to be reimbursed for drugs under federally financed health programs. These are complicated measures and raise many questions for which the answers are notably lacking; questions over the selection of drugs for the proposed formulary; the propriety of forcing the use of generic terminology; the prospect of government price fixing of drugs; the adjudication of "acceptable quality" by the federal formulary committee, and the enormous administrative burden which the bills entail.

The effects of the legislation, in our opinion, would be a reduced quality of medical care and direct government intervention in the practice of medicine. For many Americans, it would no longer be a case of the patient's best interests being served according to his individual needs and the physician's judgment. Rather, the therapy available at government expense would be determined by committee. The physician would find himself facing the dilemma of whether to prescribe a drug from the formulary so his patient could be repaid, even though he did not regard it as the most desirable drug, or of prescribing a drug not listed in the formulary because he knew it best to fit the individual circumstances, thereby penalizing his patient financially.

In addition, the establishment of two classes of citizens would also be written into the laws of the United States under these measures. To require physicians to use "generic" drugs for their less fortunate patients would create an unethical double standard of therapy. One class would get those medications which the physician knew were best and in which he had confidence; the other would get those drugs listed in the formulary by the committee.

We mention the legislative proposals in this statement because of their close ties with the issue of generic equivalency about which this Subcommittee has

heard volumes of testimony. Introduction of the legislation has heightened the importance of your work and the conclusions you reach.

We urge you to be wary of over-simplified answers to very difficult questions, and of highly colored expressions of opinion, betraying extreme prejudice on occasion.

The miracle of modern medicine owes much to the pharmaceutical advances of the last 30 years. An amazing 75% of the 200 drugs most commonly prescribed today were unknown just a decade ago. The products of quality-conscious, research-oriented manufacturers have all but revolutionized the practice of medicine, relieving suffering, prolonging life and serving as a boon to patients everywhere in the treatment of their ills. Quite frankly, we are fearful of any developments that seem to threaten the future of this unrivaled pharmaceutical system by relegating quality and drug innovation for tomorrow to secondary consideration, by placing unwarranted and unscientific emphasis on cost, and by insisting all drugs must be the same, regardless of the manufacturer's standards or the conditions under which they are produced.

As physicians, we cannot stand idly by while the nation is urged to embark on what we are convinced would be an ill-conceived therapeutic misadventure. Our purpose here has been to offer our views on this subject, the administration of drugs, which has been a major factor in professional lives for a great many years.

Again, we urge you to support our serious judgment that the relative efficacy of drugs has no scientific basis, and that required generic or formulary prescribing would be detrimental to the public health and welfare.

Sincerely,

ROBERT E. HOWARD, M.D., *President.*

APPENDIX II

CORRESPONDENCE FROM JOHN L. LACH, PROFESSOR OF PHARMACY, UNIVERSITY OF IOWA, TO SENATOR NELSON, DATED JUNE 16, 1967, WITH ACCOMPANYING STATEMENT AND BIOGRAPHICAL MATERIAL

THE UNIVERSITY OF IOWA,
Iowa City, Iowa, July 16, 1967.

HON. GAYLORD NELSON,
U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: You are no doubt aware that, subsequent to my correspondence with you requesting an opportunity to appear before your Subcommittee on Monopoly on June 7 and 8, I phoned your office on June 5 to determine whether it would be possible to accommodate me on either of those dates.

In your absence on the date of my call, I talked with Mr. Cherkasky of your staff who informed me that the schedule of hearings as presently planned would not permit an appearance prior to my departure for Switzerland on June 21. It is my understanding from conversation with Mr. Cherkasky that additional hearings will be held in the month of June and that hearings may be continued throughout the next seven or eight months.

I am disappointed that it will not be possible for me to appear before your Subcommittee at this time. As indicated in my letter, I deem it to be of great importance to the conduct of these hearings that experts in the scientific and technical aspects of the issues under consideration have an opportunity to present their views. It is my strong conviction that the hearings, to date, have placed undue emphasis on economic factors. There are other important considerations in the comparison between drug products which must be considered by your Committee in order to establish complete objectivity and fair balance in the testimony or statements presented. The fact that it was not possible for me to appear on the dates requested does not alter my interest or concern and it is for this reason that I am writing to you at this time.

The enclosed statement was prepared for the express purpose of documenting some of the scientific evidence which exist concerning comparative quality of drug products. It is a statement which I believe deserves very careful consideration by you and the members of the Subcommittee. Because of its importance, I respectfully request that the statement be made a part of the official records of the hearings and that appropriate reference be made to it during those portions of the hearings which may deal with the subject of generic or therapeutic equivalency. A personal presentation would, of course, be more informative for the

Subcommittee but in the absence of such an opportunity, due consideration by you and members of the Subcommittee will help to assure the objectivity and fair balance I mentioned earlier.

I have also enclosed a biographical sketch and a list of publications in support of my qualifications.

I trust that submission of this statement for the record will in no way prejudice my chances for an opportunity to appear before the Subcommittee at some later date should hearings continue after my return from Switzerland. If in fact, the hearings do extend beyond December, I would respectfully request at this time that I have an opportunity to personally present a statement as soon after my return as possible.

Sincerely yours,

JOHN L. LACH,
Professor of Pharmacy.

JOHN L. LACH

Birthplace: Blairmore, Alberta, Canada, February 10, 1927; U.S. Citizen, Registered Pharmacist (Iowa).

Education: B.Sc. Pharmacy, University of Alberta, 1950; M.S. Pharmacy, University of Wisconsin, 1955; Ph.D. Pharmacy, University of Wisconsin, 1954.

Married: Wife: Carol, born in Milwaukee, Wisconsin; B.A. in Education, University of Wisconsin, 1950.

Children: 3 girls, ages 13, 10, and 6; 1 boy, age 3.

Professional Experience: After receiving the Ph.D. degree under Dr. T. Higuchi, I was appointed instructor in pharmacy at the University of Wisconsin, February to June 1954; appointed assistant professor, College of Pharmacy, University of Iowa, July, 1954; appointed professor of Pharmacy, July, 1962.

Experience is mainly in the area of undergraduate and graduate instruction. I was actively involved in the revision of both curriculums including our hospital pharmacy program.

Experience also includes the manufacturing area in that I served as co-ordinator (January, 1954 to July, 1965) of this division. Duties involved a complete reorganization of this area with respect to revision of product master formulas, production control, and quality control.

Membership: American Chemical Society, American Pharmaceutical Association, Iowa Pharmaceutical Association, U.S.P. Division Committee 1960 to 1965, Sigma Xi, and Rho Chi.

Other Activities: Member of the University of Iowa Faculty Council and other university committees; Member of several A.A.C.P. committees; Member of Official Church Board of the First Methodist Church, Iowa City; Served as chairman and speaker for a number of our seminars sponsored by the College of Pharmacy for the pharmacists of Iowa.

JOHN L. LACH PUBLICATIONS

1. Investigation of Some Complexes Formed in Solution By Caffeine.

IV. Interactions Between Caffeine and Sulfathiazole, Sulfadiazine, p-Aminobenzoic Acid, Benzocaine, Phenobarbital and Barbitol (J. Am. Pharm. Assoc. (Sci. Ed.), June 1954).

2. Investigation of Some Complexes Formed in Solution By Caffeine.

V. Interaction Between Caffeine and p-Aminobenzoic Acid, m-Hydroxybenzoic Acid, Picric Acid o-Phthalic Acid, Suberic Acid and Valeric Acid (J. Am. Pharm. Assoc. (Sci. Ed.), Sept. 1954).

3. Investigation of Complexes Formed in Solution By Caffeine.

VI. Comparison of Complexing Behaviors of Methylated Xanthines with p-Aminobenzoic Acid, Salicylic Acid, Acetylsalicylic Acid and p-Hydroxybenzoic Acid (J. Am. Pharm. Assoc. (Sci. Ed.), Sept. 1954).

4. Study of Possible Complex Formation Between Macromolecules and Certain Pharmaceuticals.

III. Interaction of Polyethylene Glycols with Phenobarbital, Barbitol, Pentobarbital, Resoreinol, Catechol, Phenol, p-Hydroxybenzoic Acid, Salicylic Acid and o-Phthalic Acid (J. Am. Pharm. Assoc. (Sci. Ed.), Sept. 1954).

5. Study of Possible Complex Formation in Aspirin-Polyethylene Glycol Suppositories (Drug Standards, Jan.-Feb. 1956).

6. The Chromatographic Separation of Morphine from its Degradation Products (J. Am. Pharm. Assoc. (Sci. Ed.), Sept. 1956).
7. Study of Complex Formation of Dimethylurea with Some Pharmaceuticals (J. Am. Pharm. Assoc. (Sci. Ed.), Oct. 1957).
8. Study of Moisture Vapor Transmission Through Closures (J. Am. Pharm. Assoc. (Sci. Ed.), Jan. 1958).
9. Determination of Chlorobutanol in Pharmaceuticals by Amperometric Titration (J. Am. Pharm. Assoc. (Sci. Ed.), Jan. 1958).
10. The Chromatographic Separation and Determination of Diphenylhydantoin and Phenobarbital (J. Am. Pharm. Assoc. (Sci. Ed.), Jan. 1958).
11. Study of Possible Complex Formation of Polyoxylstearate 40 with some Pharmaceuticals (Drug Standards, Sept. 1957).
12. A study of Ascorbic Acid Tablet Formulations (Drug Standards, Nov. 1958).
13. Interaction Between High Molecular Weight Polyethylene Glycols and some Pharmaceuticals (Drug Standards, Jan. 1959).
14. The Kinetics of Degradation of Chlorobutanol (J. Am. Pharm. Assoc. (Sci. Ed.), July 1959).
15. The Influence of Various Complexing Agents on Benzocaine Degradation (Drug Standards, July 1959).
16. Stability of Morphine in Aqueous Solution.
 - I. Formulation of a Stable Morphine Solution (J. Am. Hosp. Soc., Feb. 1960).
17. Quantitative Separation of N-acetyl-p-Aminophenol and p-Aminophenol by Ion-Exchange Chromatography (Drug Standards, March 1960).
18. A Note on the Quantitative Ion Exchange Chromatographic Separation and Determination of Para-Aminosalicylic Acid (Drug Standards, May 1960).
19. Determination of N-Acetyl-p-Aminophenol in some Pharmaceuticals (Drug Standards, July 1960).
20. Separation of Morphine from Its Degradation Products (J. Am. Pharm. Assoc. (Sci. Ed.), Nov. 1960).
21. Kinetics of Morphine Degradation in Aqueous Solution (J. Am. Pharm. Assoc., (Sci. Ed.), Nov. 1960).
22. The Kinetics of the Degradation of N-Acetyl-p-Aminophenol in Aqueous Solution (J. Am. Pharm. Assoc., (Sci. Ed.), Feb. 1961).
23. "Buffers in Pharmacy" (Proc. Amer. Assoc. Coll. Pharm. Teachers' seminar 1961).
24. Interaction of Pharmaceuticals with Schardinger Dextrins.
 - I. Interaction with Hydroxybenzoic Acids and p-Hydroxybenzoates (J. Pharmaceutical Sciences, Feb. 1963).
25. Interaction of Pharmaceuticals with Schardinger Dextrins.
 - II. Interaction with Selected Compounds (J. Pharmaceutical Sciences, Feb. 1963).
26. Gas Chromatographic Separation of Amines by Special Selectivity (J. Pharmaceutical Sciences, Nov. 1963).
27. Interaction of Pharmaceuticals with Schardinger Dextrins.
 - III. Interaction with Mono-Halogenated Benzoic Acids and Aminobenzoic Acids (J. Pharmaceutical Sciences, Jan. 1964).
28. Schardinger Dextrin Interaction.
 - IV. Inhibition of Hydrolysis by Means of Molecular Complexation Formation (J. Pharmaceutical Sciences, Aug. 1964).
29. Rapid Method for the Determination of Mixtures of p-Hydroxybenzoate Esters by Gas Chromatography (J. Pharmaceutical Sciences, March 1965).
30. Spectrophotometric Determination of Some Quaternary Compounds (J. Pharmaceutical Sciences, Oct. 1965).
31. Kinetics of Hydrolysis of Monothionsuccinimides (J. Organic Chemistry, Nov. 1965).
32. Interaction of Pharmaceuticals with Schardinger Dextrins.
 - V. Interaction with a series of Phenyl-Substituted Carboxylic Acids (J. Pharmaceutical Sciences, Dec. 1965).
33. Diffuse Reflectance Studies of Solid-Solid Interactions.
 - I. Interactions of Oxytetracycline, Phenothiazine, Anthracene, and Salicylic Acid with Various Adjuvants (J. Pharmaceutical Sciences, Dec. 1965).
34. Interaction of Pharmaceuticals with Schardinger Dextrins.
 - VI. Interactions of β -Cyclodextrin, Sodium Deoxycholate, and Deoxycholic Acid with Amines and Pharmaceutical Agents (J. Pharmaceutical Sciences, Jan. 1966).

35. Effect of a Pantothenic Acid-Deficient Diet on Monamine Oxidase (MAO) and Deoxyribonucleic Acid (DNA) in Rat Liver (J. Pharmaceutical Sciences, Jan. 1967).

36. Diffuse Reflectance Studies of Solid-Solid Interactions.

II. Interaction of Metallic and Non-metallic Adjuvants With Anthracene Prednisone and Hydrochlorothiazide (J. Pharmaceutical Sciences, Oct. 1966).

37. Diffuse Reflectance Studies of Solid-Solid Interactions.

III. Interaction Studies of Oxytetracycline with Metallic and Non-metallic Adjuvants (J. Pharmaceutical Sciences, Oct. 1966).

38. Comparative Hydrolytic Rates of N-Substituted 6-Amino-thiouracils (J. Pharmaceutical Sciences, May 1967).

PAPERS TO BE SUBMITTED

1. Kinetics of Meperidine Degradation.

2. Synthesis and Antifungal Activity of Some Halogenated Diphenolic—In print.

3. Kinetics of Glutethimide Decomposition—In print.

4. The Effect of Schardinger Dextrin on the Hydrolytic Rate of O, M and P-ethylaminobenzoate.

STATEMENT OF DR. JOHN L. LACH

I am Dr. John L. Lach, Professor of Pharmacy in the College of Pharmacy, University of Iowa. I have previously served as an Assistant Professor and Associate of Pharmacy at that institution, and also served as an instructor in pharmacy at the University of Wisconsin after securing my Ph.D. degree there. Well known to the Chairman of this Subcommittee is the fact that the University of Wisconsin is considered one of the leading research centers in the world in the field of physical pharmacy.

For the past several years my special field of interest in pharmaceutical research has been the application of physical-chemical principles to pharmaceutical systems involving stability studies, complex formation, formulation and analytical techniques, and more recently drug excipient interactions in dosage forms.

I appreciate the privilege that has been extended to me to submit my views, for your consideration, on certain aspects of the important questions before this committee.

For some time physicians, pharmacists and the general public have been subjected to considerable discussion of a widely proposed answer to the rising costs of federally financed health care programs—namely, the prescribing of generic drugs as one means for holding down the expenditure of tax funds for the care of the elderly and welfare recipients. These discussions have not only appeared in professional and trade journals but also in the lay press. A good deal of it has taken place on the floor of Congress.

In the time I have today, it is not my purpose to try to examine the entire generic issue. Rather, I will limit my discussion to the subject of "generic equivalency," about which you have heard much and doubtless will hear more during the course of these hearings.

With all the sincerity I can muster, I would like to ask you to delve deeply into this matter for so much depends on it in reaching sound and objective conclusions in the overall controversy.

Before there can be a realization of the full implications of what is being proposed, for example, I believe there must be a much broader understanding than now exists as to what goes into the manufacture of a quality dosage form or pharmaceutical product.

There are the raw materials, of course, but there is more. Quality and therapeutic effectiveness must be built into the drug product by the manufacturer through each step in the formulation process. The public, members of the health team, and, yes, members of Congress, must be educated to the fact that manufacture of a quality drug product or dosage form involves many aspects other than a minimum knowledge of how to make a tablet, a suspension, an injectable or solution. An awareness and recognition and an understanding of these other factors is absolutely essential before one can objectively examine the term "generic equivalent." It is indeed unfortunate that this term has been so frequently used, not only by people in government but by physicians and pharmacists—unfortunate in the sense that these individuals have applied this generic term to dosage forms—one which was never intended.

The question of so-called "equivalency" arose the first time a drug product became available from more than one source.

To each new drug discovered (which already has a precise chemical name) a generic name or nonproprietary name is chosen as the common name for the drug. For example, "Prednisone" the generic name for the chemical compound 17,21-Dihydroxypregna-1,4-diene-3,11,20-trione. Upjohn's product of this chemical is Deltasone which is a trade name. Deltasone is a trade name for a finished dosage form containing this chemical or steroid.

This generic or common name is required by federal law. Now, while a generic name has nothing to do with the finished product or with the quality, somehow the expression "generic equivalent" has come to be used erroneously to imply equivalent quality, not only of the drug itself but of the dosage form.

A pharmaceutical company does not simply sell a drug in its basic chemical form. It sells one or more dosage forms of the drug. A compressed tablet of a given drug sold by company X is not necessarily equivalent to a compressed tablet sold by company Y in spite of the fact that each tablet contains the same active ingredient.

For purposes of this discussion, suppose you and I were asked to make an aspirin tablet—and to make ourselves as "equivalent" as possible we are told that we can use the same manufacturing equipment and the same lot of the pure aspirin or acetylsalicylic acid chemical. Let us here also suppose that the two batches of tablets prepared are labelled A and B. The question we, as drug specialist should ask ourselves is—just how equivalent are the two lots of tablets? The only thing equivalent is that we both used the same aspirin chemical and the same manufacturing equipment—and it stops here. Not only will there be a significant difference in the excipients and fillers used by both of us since this choice is not part of any regulation but also to (a) the method used in preparing the granules prior to compression of the tablet, (b) the amount of pressure used in the tableting operation, (c) the amount of aspirin in each tablet since decomposition of this chemical does occur during the manufacturing operation, and (d) the availability of the aspirin to the patient once taken.

I would, for the next few minutes, like to examine this "generic equivalent" term more closely by citing actual examples taken from clinical and pharmaceutical journals. But before I do let me quote from Dr. Nelson's and Levy's paper which appeared in the *Journal of the American Medical Association* (1) dealing with *Pharmaceutical Formulations and Therapeutic Efficacy*. They state that, and I quote, "Formulations of drugs into various dosage forms may modify profoundly the onset, intensity, and duration of physiologic response. It may also modify the correct dosage required by the patient, the incidence and intensity of side effects and the stability of the drug. Because of these modifications it is clear that in some cases choice of dosage form and manufacturer's brand may be as important as the choice of the actual therapeutic agent."

There are many factors which go into the manufacture of a quality and therapeutically active drug product. Dr. Max Sadove (2), a clinical researcher of the Veterans Hospital in Chicago, with some twenty years experience in drug evaluation lists some twenty-four factors. Time does not permit a discussion of all these, however, I would like to mention the more important ones—potency; compatibility; purity; drug availability; drug solubility; effect of vehicle, base or other ingredients; quality of active ingredient; particle size; dissolution rate; stability; pH; and viscosity.

Differences in therapeutic efficacy among different generically equivalent dosage forms are often due to differences in the date at which the active ingredient or ingredients become available for absorption. This difference in the rate of absorption may greatly modify the onset, intensity and duration of the desired physiological response. Not only is this response modified but depending on the degree of absorption of the therapeutic agent from the dosage form, the incidence and intensity of side effects from the drug may also be altered. This difference in therapeutic efficacy may also be due to lack of stability, contamination and to sub-potent preparations. What I'm saying is simply this—the drug must be in solution and absorbed to be therapeutically effective. Factors then such as particle or crystal size, disintegration time, dissolution rate, etc., all have a tremendous bearing with respect to this absorption rate. Let me illustrate with some examples.

A European pharmaceutical firm (3) was asked to increase the physical size of their Dicumarol (bishydroxycoumarin) tablets to facilitate breaking the tablets for administration of half doses. This they did easily by just making the tablet larger. Patients who switched from the smaller tablets to the larger ones

(containing the same amount of dicumarol) required larger doses in order to maintain prothrombin levels in the therapeutic range. Why? Laboratory tests showed that the rate of dissolution of the drug from the larger tablets was much slower than from the smaller tablets. Yet there was no change in the amount of drug but only in the amount of excipients used to produce this larger tablet. So the tablets were reformulated to increase this rate of dissolution of the drug. Yet it was discovered that some patients, who had their prescription filled with these new tablets still showed prothrombin levels below the therapeutic range. The only solution here was to have the physician retitrate the patients with respect to their dicumarol requirement for that tablet or dosage form.

It is quite likely that no two manufacturer's brands of dicumarol tablets will act alike in therapeutic activity and it is conceivable that a change from a slow release brand to a fast release may be extremely detrimental to the patient.

Every tablet obviously must disintegrate and release the medicament in a manner which makes the drug available for absorption. For the treatment of certain emergency conditions, such as an asthmatic attack, it is important that the tablet disintegrate rapidly and release the drug. On the other hand, where tablets contain drugs which may produce gastric irritation on rapid release of concentrated drug quantities, it is important that this disintegration and release of drug not be too rapid.

A study conducted by Chapman and co-workers (4) which appeared in the Canadian Medical Journal dealt with the disintegration time of twenty-nine tablets of two different drugs and found that sixteen of these took longer than sixty minutes to disintegrate. The tablets were still intact and the drug present in a form not available for therapeutic activity. The authors state that, "While it is relatively simple to assay a preparation and ensure that it meets labelled claim, it is more difficult to determine whether the drug is available to the patient once administered."

In a later study the same author (5) examined the absorption characteristics of riboflavin tablets. Generally speaking, the data showed that the riboflavin tablets showing the longest disintegration time were least absorbed—one to the extent of less than 14%. A drug must be absorbed in order that a therapeutic response be obtained.

An interesting study and one I want to mention here is one recently completed by the Food and Drug Directorate of Canada (6). This agency examined some ten different hydrochlorothiazide tablets produced by ten different manufacturers. They report that $t_{1/2}$, that is the time necessary for the tablet to dissolve and release 50% of its drug into solution varied from some two minutes to over five hours from these various tablets. The important point here was the fact that all of the tablets contained the same amount of drug and that all of the tablets disintegrated within the sixty minute time limit set down by the USP. Release of the drug from the disintegrated particle was another matter. The tablets here were equivalent—equivalent in the sense that they all contained the same amount of drug—but certainly not equivalent in their ability to release the drug to the patient for the required therapeutic response.

An increase in the pressure used in the compression of tablets, which is reflected by an increase in the disintegration time and medicament release, may markedly influence the intensity of the therapeutic effects and the availability of the drug. Again studies (7) have shown that substantially different blood levels vs. time curves were obtained when various penicillin V tablets compressed at different pressures and having different disintegration times were assayed *in vivo*. It should be noted here that at sixty minutes, which is the upper disintegration limit set by the U.S.P., only about 60% of the drug was available for absorption. Beyond sixty minutes the patient was in effect getting a placebo since the amount of drug released from these particles was below a therapeutic level.

Another rather dramatic example of marked potency difference involved Prednisone tables (8, 9). This is of particular interest to me in that we had a similar experience at the University of Iowa. Prednisone, as you are aware, has been one of the drugs which was the subject of much public discussion in Washington with respect to equivalency of product irrespective of the manufacturer.

Certain published reports involved prednisone tablets prepared by two manufacturers. Both showed the same prednisone content by laboratory analysis and both disintegrated into small particles in the time set forth by the U.S.P. Yet only one tablet gave the expected physiological response when administered to patients—the other was inactive. Why? The difference here was in a formula-

tion know-how—a know-how by one manufacturer to formulate in such a manner that the tablet not only disintegrated but released its drug for absorption and a physiological response. What detrimental effect this lack of therapeutic response had on the patients in this report I do not know. I do know, however, this detrimental effect with respect to the case I was personally involved in and I might say that it was a serious one. A change from a trade name brand to a generic one did save this patient several dollars at a cost of permanent physical body damage.

One way of administering the large doses of p-aminosalicylic acid needed in the treatment of tuberculosis with minimum discomfort to the patient is to prepare granules with shellac or other coatings. Now the availability of the drug from shellac coated granules decreases with age of the granules and after some time the blood levels attained are usually below the minimum therapeutic concentration. Since there are no standards for such coatings it again should be obvious that various brands of coated PAS granules cannot be considered equivalent—equivalent only in the sense that these products may contain the same amount of the drug. But certainly not equivalent with respect to clinical efficacy.

The effect of dicalcium phosphate and other metallic salts in depressing tetracycline absorption is well known to members of the profession of pharmacy. Prior to the time that this effect was known, interchanging brands of tetracycline made large differences in blood levels and therapeutic effects obtained and was discouraged. Why? Here obviously the filler materials used had some marked effect on the product. Again we can ask ourselves this generic equivalent question. The products all contain tetracycline—why then should some inert excipient material prevent us from making the statement that these products aren't generically equivalent.

I would like to digress here for a few moments and point out some research that my students and I have been engaged in at the College for the past several years. We, as pharmacists, have been extremely interested in this question of generic equivalency. The increasing number of reports dealing with the therapeutic discrepancies of a drug in tablet form prepared by various firms certainly suggested that all tablets containing a certain drug do not behave alike. It was our belief that these discrepancies must be due to more than just effects of disintegration times, method of manufacture, size of drug particle and so on. We felt that, since many of our drugs are complex sophisticated molecules containing many functional groups capable of undergoing interaction or reactions with the various fillers that these interactions or complexes would occur when a tablet was manufactured and compressed. Our research started out with dogs which have been reported to show these therapeutic discrepancies. I've already mentioned some of these, for example, diuril, tetracycline and prednisone.

We have, for the first time by chemical and spectrophotometric methods (10), been able to show that drugs, such as those I've mentioned, do undergo surface chemical reactions with the fillers or so-called inert materials used to prepare these tablets. For example, tetracycline reacts chemically with the surface of the insoluble dicalcium phosphate filler used in the manufacture of such tablets. Such a complex keeps the drug tightly bound so that it dissolves at such a slow rate that no therapeutic level is obtained for the necessary physiological response. Prednisone undergoes similar surface interactions with many of the common filler materials used in the manufacture of solid dosage forms. This prednisone-excipient or filler interaction would certainly account for the lack of therapeutic response I mentioned earlier. Diuril also undergoes this type of interaction.

Our research with these and many other drugs point out that this type of interaction is common and that it depends on what type of filler is used.

One then, in formulating a tablet, does so as to minimize this effect by a scientific approach to this selection of excipient material.

The drug manufacturer, striving for the highest quality in his products, not only recognizes that these undesirable drug-excipient complexes may exist and formulates in such a way as to avoid these but also sends the product to the clinic to be absolutely sure the drug does give the desired therapeutic response. This type of approach is not only expensive but one that is absolutely necessary from the patient's point of view.

Can the generic house formulate in this manner and still produce cheap therapeutically active drugs? Some in Washington unfortunately think so.

This problem of clinical or therapeutic efficacy of drug products is a question which all members of the health team must be concerned with now and not the

cheapness or the price. At least not until the F.D.A. demands this "clinical efficacy" requirement for all drug products manufactured and sold.

Let us continue with several more examples of pharmaceutical dosage forms where this equivalency term should be questioned. The area of sustained release medication and enteric coated materials should be mentioned. Many studies have shown that the rate of release of drugs and subsequent absorption and therapeutic response varies tremendously for such dosage forms prepared by various firms. For example, a study (11, 12) on the rate of release of dextroamphetamine sulfate in sustained release dosage forms of a number of companies showed that no two products behave alike. Some products released the entire twelve hour supply in less than three hours—others released only 30% of the drug in this time. Dextroamphetamine sulfate is a potent drug. A drug response designed for a twelve hour period produced in less than three hours is one, I'm sure, the patient or for that matter the physician didn't expect. The important point here is that all of the products contained the same amount of drug and all supposedly were generically equivalent.

Since there is, as I've already mentioned, no uniformity or for that matter no standards with respect to the coating used for the preparation of enteric tablets, it is not surprising then to find, in the literature, a wide variation in the activity of such products. Reports show that some of these so called enteric coated tablets dissolve rapidly in the stomach with extreme discomfort to the patient—a product not meant to dissolve here. Other products go right through and are recovered intact. Such a coating, I'm sure, should be investigated and would have tremendous potential in fields other than therapy.

So far, I've dealt with tablet formulations primarily. What about other dosage forms such as ointments, suspensions, etc.

Let me say here that these same considerations apply. Again the medical and pharmaceutical literature lists many reports of such therapeutic discrepancies.

I should like to point out that such factors as suspending agents, surface active agents, particle size, fillers and so on, all have a tremendous effect with respect to the therapeutic efficacy of a drug product. In addition, such surface interactions as those that I pointed out for tablets, also manifest themselves in suspensions and ointments. Studies have shown that not only the type of vehicle—oil or water—is important but also the type of drug salt used with respect to therapeutic activity and proper blood levels of the drug.

The antibiotic novobiocin exists in two forms, an amorphous and a crystalline form. Only the amorphous form is biologically active (13). In aqueous suspensions the amorphous form changes to the inactive crystalline form. Only an awareness of this and the use of special manufacturing techniques ensures a quality product, a biologically active product. Some products of this antibiotic may have been sold in the crystalline inactive form. Chemical analysis cannot distinguish between these two crystalline forms. So consequently a chemical analysis of a product stating that the drug is present in the labelled amount means nothing. In this case only a biological assay will show whether the product is active or not. Yet comparable products would be considered to be generically equivalent.

The type of bases used in ointment preparations, as you know, is very important with respect to the rate of release of a medicament. For example, it has been shown (14) that the rate of release of aspirin in a carbowax or polyethylene glycol base was approximately 95% of that obtained from oral absorption—from a cocoa butter base 66% and from a glycerinated gelatin base only 53%.

This high degree of absorption from a PEG base looked interesting—interesting enough for one of our drug firms that they marketed a phenobarbital suppository in this same base. After the product was on the market for some time, and much to their embarrassment, they were told that the therapeutic effect was missing. Chemical analysis showed the phenobarbital to be present and, oh yes, the suppository did dissolve. Why then the lack of therapeutic activity? Research conducted in our laboratory provided the answer.

In the case of the PEG-aspirin suppository the aspirin interacted with the PEG to form a soluble complex, a complex which was rapidly absorbed.

On the other hand, in the case of the phenobarbital-PEG suppository, the phenobarbital also interacted with this base only to form a very insoluble complex, a compound which was not absorbed.

It was pointed out to me here that all was not lost, at least from the patient's point of view. He did get an effect even though it was a psychological one.

The point here is simply this—one cannot use these bases indiscriminately, one

has to know whether the drug exists as such in a base or whether it has undergone some reaction with it. And, is the resulting product therapeutically active?

With respect to ointment bases Lafferty and Gross (15) reported that it had been established that the particle size of medicinals dispersed in ointment bases has a direct influence on tissue irritation, drug absorption and the therapeutic efficacy of the medicament, but that, "The examination of competitive products indicated a wide range of control or lack of control of particle size between various manufacturers of the same product." They studied many ointments, to name but a few, boric acid, zinc oxide and mercuric oxide, all U.S.P. They conclude by saying that here is another example where dosage forms can meet official requirements in active ingredient content yet vary widely in certain important characteristics, depending on the skill of the manufacturer.

To me, this is not surprising since we have no regulations governing such things as the type of fillers one can use, the size of the drug particle permissible, and so on. Yet such things are of extreme importance with respect to the performance of the finished drug product.

These are but a few examples of how drug products can be generically equivalent and yet be so generically unlike with respect to their biological activity or performance.

Now that we have established the fact that there is a definite difference in similar drug products and that this difference may exist with respect to trade name products and generics let us examine the point even more closely. Let us take a common drug product—a generic one, Prednisone.

An examination of the Red Book reveals that some eighty-seven drug firms produce, not the drug chemical itself but the finished dosage form. Pharmacists have eighty-seven different sources for this product and the price for this product is going to vary.

How then could I be sure of any of these eighty-seven products? This I'll try to answer later.

Getting back to these eighty-seven companies producing the tablet form of this drug, how many of these same companies market an ophthalmic ointment or an injectable?

The answer is very simple—only a few.

Why? Again the answer is simple.

It costs money to produce sterile ophthalmics and sterile injectables, the profit margin would be too small when compared to a trade name product. And, of course, the market for this type dosage form isn't as great as that for tablets. There is more money to be made in the tablet area and also one doesn't have to bother with sterility control or special equipment and manufacturing procedures.

Thus, when pharmacists handle generic products or trade name drugs unfamiliar to them, they must consider the following:

(a) Is this product "equivalent" in all aspects to an established and therapeutically effective product they are familiar with.

(b) They must not be misled by some company advertisements which state that all its products are chemically assayed or that analytical data will be sent on request. This, in itself is meaningless with respect to the therapeutic activity of the drug product.

(c) They should ask for absorption and excretion data, blood level data or any clinical data available. This is usually available for quality products. Only with this type data can the pharmacist be reasonably assured that the product is therapeutically active.

Pharmacists have a responsibility, not only to the physician and patient, but also to the drug industry which is in business to develop new drugs and to produce quality drugs and therapeutically effective drug products.

Let me, at this point, touch briefly on some of the comments which have appeared over the past seven months in the Green Sheet of the publication "Weekly Pharmacy Reports" concerning this generic equivalent controversy. Since time does not permit any discussion, I'll just capsule these.

Enforced generic system for welfare prescriptions under federal-state medicare program by-passed by HEW Department after fifteen months of vigorous internal discussion.

The cheapest or lowest-cost-drug concept has been all but eliminated for generic drug legislation in the 90th Congress. Senator Montoya's bill introduced January 11 would pay for the lowest cost drugs * * * which is of a quality acceptable to a Formulary Committee to be established under a separate bill.

Compulsory generic prescribing on government programs not feasible until *clinical equivalency* is proven. Both F.D.A. Commissioner Goddard and Surgeon

General Stewart are interested in getting funds to start clinical equivalency studies of drug products. * * * (I'm sure this was not their thinking of a year ago.)

Pro-generic Senators Long and Montoya want to develop a compendium that would stress the "lowest cost" drugs of the best quality for federally sponsored medical programs.

Unfortunately true F.D.A.'s Goddard tells house committee when asked whether comparing drugs by generic name is like comparing a Model-T to a Cadillac.—Goddard was appearing before "get acquainted" hearings held by the Interstate Committee, when Representative Nelsen asked him: "It has come to my attention that, for example, to compare a drug by a generic name would be like comparing a Model-T to a Cadillac, and the effectiveness of a drug of a similar generic name may not be exactly the same." Nelsen continued his questions: "Then when you get into the prescribing of a drug, is it true or is it not true that there may be a variation as to the effectiveness of a drug of a similar generic name, ignoring trade or brand name?" "Yes," Goddard replied. "This is unfortunately true. I say unfortunately, because it means we are not performing our functions as well as we have to. We view our goal as being one where the physician can prescribe any drug that is in the market place on any basis he wishes in terms of whether he uses brand names or generic names, and be assured that those drugs are all effective and they are safe. This is not the case today and there is variation. The Defense Supply Agency in its procurement program for drugs has clearly demonstrated differences between brands and we have seen some of this."

Need I say more * * *

Most physicians know very little about the formulation of drugs for clinical use. They assume that the Food and Drug Administration, the United States Pharmacopeia and the National Formulary exert the necessary controls and that therefore, when the product is ready for clinical use, it represents an accurate amount of drug which is clinically or therapeutically effective. This is, as we have seen, not always true.

It is obvious then, that there is a definite need for these agencies to enlarge their interest in the formulation of stable, safe and therapeutically active drug products.

Until this comes about, the public, the medical profession, pharmacy and the drug industry must seriously concern themselves with this problem of "cheap drugs".

I would like to conclude by saying that a *therapeutically inactive* drug product no matter how cheap, whether it be a generic or a brand name is an *expensive* drug for the patient be he on a privately or government sponsored health program.

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APPENDIX III

CORRESPONDENCE FROM DR. CLARENCE L. GANTT, ASSOCIATE PROFESSOR OF MEDICINE AND ASSISTANT DIRECTOR OF CLINICAL RESEARCH CENTER, UNIVERSITY OF ILLINOIS, TO SENATOR NELSON, DATED OCTOBER 19, 1967, RE DRUGS

UNIVERSITY OF ILLINOIS,
COLLEGE OF MEDICINE,
Chicago, Ill., October 19, 1967.

Senator GAYLORD NELSON,
Chairman, Subcommittee on Monopoly,
Senate Select Committee on Small Business,
Washington, D.C.

DEAR SENATOR NELSON: The problems of the cost of drugs in the U.S. presently under consideration by your distinguished subcommittee are of such magnitude and importance, both now and for at least a generation to come, that I wish to offer some comments on these matters. Please be assured that my remarks are intended only to assist your distinguished group in this very complex mixture of science, sociology and economics. Since I am neither a sociologist or an economist, I will limit my remarks to the area that I can make responsible judgments—the scientific.

I am a physician, Board Certified in Internal Medicine, an endocrinologist, an Associate Professor of Medicine, and a clinical investigator, working with both humans and animals. A great deal of my work is in the field of animal and human pharmacology. The remarks are entirely my own and are not to be related to the College of Medicine, University of Illinois.

Backing far enough away from the problem to be able to at least find the forest, one is first struck by a fact of medical history. Except for a very few isolated individuals, the academic community many years ago turned over to an industry the search for new therapeutic agents. The academicians have until very recently looked down on their colleagues who were interested in new agents. This atmosphere still persists to a lesser degree today. Therefore, for good or bad, the only real source of therapeutic agents today is the pharmaceutical industry. As the complexities of chemical synthesis and biological screening have greatly increased in the past few years, it is likely that this will be even more true for the next few decades. The academic community can not take over this function for society.

The pharmaceutical industry is a motley group composed of companies that have made very far reaching advances in the field of therapeutics; others that have acted principally as developers of others ideas; other companies that have performed chiefly as a production operation, selling items such as intravenous fluids without patent protection; still others that have acted as huge sales organizations, and lastly, other companies that have made no effort at research or development but only compounded what is easily available to be sold on a competitive price basis, keeping all production and sales costs at a minimum. It is apparent that certain aspects of this large group need to be strengthened while others need to be radically changed or eliminated. The only real advancements will come through research and an absolute premium should be placed on this.

The next point that one sees in relation to drug costs is the "development" of the profession of pharmacy, from the apothecaries, who knew and practiced a little chemistry and a lot of pharmacology, to the present corner "drug store" pharmacist who sells everything from ice cream sodas to cigarettes, cosmetics and basketballs, while increasing by approximately 100% the price of every prescription drug that he pours from one bottle to another. To double the cost of drugs just as they pass to the patient is a dear price indeed to pay for having a drug store on every corner. Still on an average there are not a lot of wealthy pharmacists, suggesting a problem of proper distribution of manpower somewhere in that profession. It is quite possible with existing technology to perform the functions of the pharmacist with a computer.

A third obvious point that is easily discerned by moving slightly closer to the problem is that relating to the United States Pharmacopeia. Many of the concepts of purity put together by the U.S.P. committees on this subject were developed before the era of effective drugs and before the techniques of chemical synthesis became so complicated. As a result of this it is generally not possible for me to use chemical reagents in the laboratory that meet only U.S.P. requirements as they are usually so impure that they invalidate our chemical tests. These facts are well known to any analytical chemist or laboratory technician. The attached price

lists¹ of chemicals pulled at random from suppliers (who do not make drugs and therefore are not involved in the drug price controversy) demonstrate very readily that if they have to go through further steps of purification beyond U.S.P. purification standards, the price is higher per unit weight. Our inability to use them in the laboratory and the price differential suggest that the requirements of chemical purity of U.S.P. chemicals are so low as to be of very questionable use in the area of human therapeutics.

The United States Pharmacopeia in cooperation with United States Adopted Names Council controls the generic or public name of drugs. For some reason they have tried to use a chemical basis for naming new drugs. The result has been names so long that most physicians can not even pronounce some of their tongue twisters, let alone remember or spell them for writing prescriptions. The contractions of chemical nomenclature that result are also of no value in deciphering the structural formulae of the compounds. For good or bad, most physicians have to use trade names short enough for them to remember in their practice.

Moving still closer to the problem of generic versus trade name drugs, we found very little scientific evidence on either side of the fence. The companies with the brand name products maintain that their products are better, while the generic equivalent companies maintain that theirs are equal but cheaper per unit. It is unfortunate, but true, that at present one is forced to rely not on scientific data, but on the gross reputation of past performance of the manufacturers in the selection of drugs for the patient.

The U.S.P. criteria are for a tablet to *contain* a drug while the experience of a company as it develops new agents indicates that the tablet *delivers* a certain pharmacologic effect. Several of the bad experiences with generic drugs have already been pointed out by others to your distinguished committee, and do not need to be repeated here. There must be good experiences with these agents also, but in the area of health it is not wise to experiment broadly.

Having no other basis other than the gross past performance of an older established company to rely on and being fully aware that the other possibility is a vast experiment too broad to foster on an aged and/or poor population group, who could not even give their informed consent to participate in such an experiment. I sympathize with you and your distinguished colleagues in this dilemma.

My suggestions would be that before you reach any conclusions in this matter: (1) wait until the special study committees on Efficacy Review of the National Academy of Science, National Research Council report to Commissioner Goddard of the Food and Drug Administration on those drugs that were on the market prior to the new F. and D.A. regulation on efficacy; (2) request that the pharmaceutical industry provide over the next few years proof that their particular brand name or generic name drug will pass certain rigidly controlled tests of blood levels of the drug, efficacy, stability, etc. so that at some point in the reasonable future there can be some scientific basis for a rational judgment; (3) study means by which to reward scientific investigations and the development of new therapeutic concepts to such an extent that this is significantly more profitable than simply marketing someone else's drug or a slight modification thereof, (my statement here is meant to be positive and not negative since being restrictive will do no good in the long run to advance medical care and this must be an overriding interest); (4) contemplate new methods of distribution such as automation to cut the very major costs created by a group that contributes nothing to the therapeutic agent; (5) determine what can be done to update the U.S.P.; (6) avoid highly inflammatory issues directed at the public, such as Dr. Burack's book since this approach generates a lot of glib opinion and little or no scientific data on which to base a rational decision, and (7) lastly develop bold new concepts that will succor the truly productive aspect of the only industry that can make new therapeutic agents available to the public, while weeding out those aspects that contribute little to the long-term advancement of the human race.

Thank you for your kind consideration of these remarks. I do hope that they can be made a part of your hearing record. I have taken the liberty of sending copies of this letter to all the members of your subcommittee.

Sincerely,

CLARENCE L. GANTT, M.D.,
Associate Professor of Medicine and
Assistant Director of Clinical Research Center.

¹ Retained in committee files.

APPENDIX IV

DOCUMENTS ON VIBRAMYCIN (DOXYCYCLINE) FROM FDA FILES

Labeling for "Vibramycin" (doxycycline HCl, Chas. Pfizer & Co. NDA 50-007)

JUNE 29, 1967.

ROBERT M. HODGES, M.D.,

Director, Office of New Drugs.

Dr. ALAN E. SMITH,

Acting Deputy Director, Division of Anti-infective Drugs.

JOHN M. DAVITT,

Pharmacologist, Division of Anti-infective Drugs.

As requested, here are the statements proposed by DAD pharmacologists for inclusion in appropriate sections of Pfizer's labeling for Vibramycin:

1. At relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

2. As with some of the other tetracycline antibiotics, gross discoloration of the thyroids, ranging in intensity from brown to black, can be produced by high oral doses of Vibramycin in several species of experimental animals. The significance of these changes is uncertain. I¹³¹ uptake studies in rats and dogs failed to demonstrate any interference with thyroid function.

The Pfizer people maintain the first statement is superfluous since both GI disturbances and evidence of hepatic effects in humans are already mentioned in the labeling.

Although they agree that the second statement is factual and belongs in the labeling, they object to its use at this time on the grounds that it would result in an unfair competitive disadvantage for their product. They have indicated willingness to include this statement in their labeling only when competitive products are similarly labelled.

JULY 31, 1967.

NDA 50-006, 50-007

MEMORANDUMS OF CONFERENCE AND TELEPHONE CONVERSATION

CONFERENCE

Present: Dr. Monroe Trout, Chas. Pfizer & Co., Inc.; Mr. Joseph P. Aterno, New York, N.Y.; and Dr. Herbert L. Ley; Dr. Edwin I. Goldenthal; Dr. Alan E. Smith; Dr. Kent Potts, FDA; Mr. Julius Hauser; Mr. Ola Bain.

Subject: Vibramycin (doxycycline) NDA 50-006 and 50-007.

Proposed changes in the label and labeling for Vibramycin as outlined in the Memo of Conference of July 28, 1967 were reviewed in detail. The Pfizer representatives objected to any changes because the requests were being made too late, they thought final agreement had previously been reached, they have already printed many package inserts and containers. Dr. Ley pointed out that antibiotics are unique in that the Commissioner, not the Bureau of Medicine, has the final judgment regarding their approval. Hence a company takes a risk if printing is started before approval of the Commissioner is granted.

Discussion proceeded to the specific changes which had been recommended. In the labeling under "Action" we had suggested that the sentence about in vitro antibacterial activity be omitted or followed by the statement: "This is of no known clinical significance". Pfizer objected as they believe this degrades the importance of in vitro sensitivity testing. Dr. Ley said he would prefer that they omit the whole thing as the differences noted were so small that we believe they are of no consequence. Other suggested changes in the package insert were considered minor by Pfizer and they voiced no specific objections.

With regard to the immediate label and carton changes the visitors strongly objected as they are using the same format for Vibramycin that they have previously used for other tetracycline products, they don't see how all the requested information can be included on the front panel, they have already printed a number of these pieces and it would be expensive and time-consuming to have them redone.

After considering all facts presented Dr. Ley offered the following suggestions:

1. The company could use their present supply of immediate labels and cartons

until the next printing or 120 days from the date of publication of the monograph for doxycycline in the Federal Register.

2. With regard to the package insert he would discuss three possibilities with Commissioner Goddard: Immediate modification, modification within 120 days of publication of the monograph with assurance that the contested areas would not be used in promotion, immediate modification now with the new insert to go in all unstuffed supplies (old insert to be left in supplies which have been stuffed). The Pfizer representatives were invited to consult their Management personnel and comment on these possibilities today.

KENT H. POTTS, M.D.

ALAN E. SMITH, M.D.

TELEPHONE CONVERSATION

Between: Mr. J. Aterno, Chas. Pfizer & Co., Inc., and Dr. Alan E. Smith, Acting Deputy Director, Division of Anti-infective Drugs.

Mr. Aterno called to say that he had met with other members of his firm, after his return to New York today (following this morning's meeting in Dr. Ley's office).

The firm has agreed to change the package insert as discussed this morning:

Under "Actions" the second sentence will be deleted in its entirety. The proposed third sentence, therefore, will not be used.

The other changes will be made.

The revised insert will be used, even in the samples already processed with a "July 1967 insert".

The immediate labels and cartons will be revised within the time limit agreed to this morning (90 days after effective date).

Typewritten copies of the revised insert will be brought on August 1, 1967.

Dr. H. L. Ley, Jr. was advised of this at about 4:15 p.m. and he requested that I notify Mr. Julius Hauser of ACC by telephone. Dr. Ley said that he thought this would obviate the need of further notification.

Mr. Hauser agreed to this.

ALAN E. SMITH, M.D.

Forms 5, NDA 50-006, 50-007

AUGUST 24, 1967.

MEMORANDUM OF CONFERENCE

Present: Mr. Jerry Avergun, Chas. Pfizer & Co., New York, N.Y.; and Dr. Max B. McQueen, Division of Anti-infective Drugs; Dr. Kent H. Potts; Dr. Alan E. Smith (part time).

Concerning: Promotional material for Vibramycin (doxycycline)

A compendium and file card were officially submitted for our review after Mr. Avergun pointed out how these differed from rough draft or mock up copies which we had previously seen, but which were not formally submitted to FDA. Mr. Avergun was told that these appeared to be satisfactory, but that his firm should await an official letter of approval before printing these or any other promotional pieces. Mr. Avergun asked when such a letter could be anticipated and was told that no definite time could be set as the approval would have to be made through administrative channels and that the time required for this would depend upon whether questions or problems arose. He seemed unhappy with this answer and said Pfizer was "heavily committed in this project." He, nonetheless, was again encouraged to await official approval before proceeding with printing.

KENT H. POTTS, M.D.

U.S. GOVERNMENT MEMORANDUM

AUGUST 31, 1967.

To: William R. Jester, Director, Division of Antibiotics & Insulin Certification
From: Deputy Director, Bureau of Medicine
Subject: Vibramycin labeling

Chas. Pfizer & Co., Inc., New York, N.Y. (AF 12-118).

"Vibramycin Capsules," NDA 50-007.

"Vibramycin for Oral Suspension," NDA 50-006.

Bureau of Medicine has checked and approves the package labeling (insert), carton and bottle labeling for these products.

All promotional labeling for these products is still under review by the Bureau of Medicine and none of this should be used by the firm until it receives our approval in writing at a later date.

Because preliminary review of the submitted promotional labeling has raised significant questions, Pfizer should be cautioned that no journal advertising should be placed regarding these products unless it is fully in accord with the approved package labeling and otherwise meets the requirements of the regulations under section 502(n).

B. HARVEY MINCHEW, M.D.

DECEMBER 22, 1967.

Mr. JACK POWERS,
Charles Pfizer & Co., Inc.,
235 East 42d Street,
New York, N.Y.

DEAR MR. POWERS: This is to confirm our telephone conversation today concerning the details of Vibramycin at a recent American Academy of Pediatrics meeting. Statements have been received from members of my staff as well as practicing physicians indicating that your firm's representatives stated that the drug was less apt to cause tooth staining because of the lower calcium binding capacity. It also stated that the drug was more effective over a larger spectrum of gram positive and gram negative organisms including certain staphylococcus and pseudomonas species, than were the other tetracyclines. Both of these statements are, of course, inconsistent with your final printed labeling and therefore false and misleading.

You indicated your willingness to clarify any existing misunderstandings by a personal letter from you to your representatives clearly stating that drug detailing will be limited to that which is approved in the final printed labeling. I would appreciate your providing me with a copy of the letter you send to your employees concerning this matter.

Sincerely yours,

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs.

APRIL 9, 1968.

Chas. Pfizer & Co., New York, N.Y. (AF 12-118)
NDA 50-006 Vibramycin, 50-007

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Mr. Charles Hagan, Chas. Pfizer & Co. and Dr. R. S. McCleery, Mr. H. W. Chadduck, Division of Medical Advertising/OMS
Subject: Vibramycin Journal Advertisement, example: MD Medical Newsmagazine, April 1968

The subject ad, consisting of a two-page spread of promotional copy plus one column on a third page presenting a "Brief Summary," was brought to the attention of Pfizer representatives at a meeting in the Commissioner's office on April 8, during a discussion of Urobiotic-250 promotion and package labeling.

Defects in the Vibramycin ad were of the same type as those in the Urobiotic-250 advertisement discussed at the 4-8-68 meeting.

This telephone conversation with Mr. Charles Hagan (Pfizer) was by way of follow-up to obtain a record of the firm's agreement to correct the Vibramycin ad defects. The gist of the information and commitments given by Mr. Hagan is as follows:

1. The above-described Vibramycin ad is not scheduled to run after April 1968.
2. Future ads will include corrections of (a) side effect statements that emphasize minimal specific side effects without calling attention to other and more serious side effects listed in the "Brief Summary" of the ad and/or package insert, and (b) broad promotional claims such as "... oral broad-spectrum tetracycline antibiotic*" without adding information qualifying the claim so as to bring out limitations of effectiveness and to make the claim more meaningful and informative. The purpose here is to provide some specificity of knowledge of drug without necessarily going into great detail at that point in the ad.

On point 2(b) above Mr. Hagan said that he would discuss with Mr. George Strong (Pfizer) the language to be used in qualifying such a claim and would telephone us on Friday, April 12, and propose language for an opinion.

3. Mr. Hagan indicated that he would send the FDA a letter in regard to Vibramycin ad and it was left that such a decision was to be that of the firm. Unless such a letter of commitment is received, however, additional attention to the ad should be considered by FDA.

H. W. CHADDUCK.

U.S. GOVERNMENT MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
April 18, 1968.

To: Max B. McQueen, M.D., Office of Marketed Drugs (MD-330)
From: William E. Dye, Ph. D., Office of New Drugs (MD-140)
Subject: Proposed labeling change for package insert for Vibramycin Capsules, Charles Pfizer dated March 1, 1968

1. This is a request to add the following sentences to the insert: "The spectrum of Vibramycin is essentially that of the other tetracycline analogues. Certain strains of organisms, including Staph. aureus, may exhibit greater susceptibility *in vitro* to Vibramycin than to the other analogues. *In vitro* susceptibility testing should be conducted.

2. There is no objection to the first sentence.

3. Although the references quoted do show some increase in *in vitro* susceptibility to Vibramycin when compared to other tetracycline analogues, I recommend that the second sentence be deleted. The effect seen could easily be a laboratory artifact based upon a difference in the stability of the analogues or to a difference in the pH at which they display maximal antibacterial effectiveness. This sentence implies that Vibramycin might be effective in clinical infections caused by tetracycline-analogue resistant Staphylococcus aureus. There is no evidence for this. If the sentence is permitted to remain, it can be expected to be the basis for advertising claims for this drug with the above implication.

4. There is no objection to the third sentence.

WILLIAM E. DYE, Ph. D.,
Clinical Microbiologist, DAD.

MEMORANDUM OF CONFERENCE

April 23, 1968.

NDA No. 50-006, 50-007

Between: Mr. Avergun, Dr. McDermott, Dr. Sikowski, Pfizer; and Dr. Ortiz, Dr. McQueen, Dr. Hurwitz, Dr. Dye, Dr. Borowsky, FDA

Dr. Hurwitz discussed the proposed labeling for Sterane. He stated that the changes were satisfactory, but a pregnancy warning was necessary. The company disagreed about the wording of the warning but agreed to consider it.

Discussion of the labeling of the proposed 20 million unit vial of Penicillin G centered on the labeling.

A supplement to revise labeling on Vibramycin was considered next. The supplement, dated March 1, 1968, inserted in the labeling words to the effect that the drug was particularly indicated for use in infections caused by staph. aureus. Dr. Dye contended that the results in the article on which this claim was based were invalid because they could well be due to laboratory artifact. He also cited an article in the American Journal of Medicine stating tetracyclines should not be used in staphylococcal infections at any time. These facts coupled with the fact that this new wording might well be used for misleading advertising claims led to FDA position that the supplement should be denied. The company disagreed, but stated they would withhold action until they received our letter.

STEPHEN A. BOROWSKY, M.D.,
Division, Meta/Endo Drug Surveillance.

U.S. GOVERNMENT MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,

June 5, 1968.

To: John J. Jennings, M.D.

From: Edwin M. Ortiz, M.D.

Subject: Memo dated May 28, 1968 from Dr. Minchew regarding Vibramycin

I would like to know the names of the Pfizer representatives who met with Dr. McCleery, Mr. Chadduck and Dr. Minchew.

Pfizer submitted a supplement to their Vibramycin form 5 (NDA 50-006, 50-007) to state under "Actions" the results of a study which showed Vibramycin to be more active *in vitro* against certain strains of staphylococci than other tetracyclines. This submission had been reviewed by Dr. Dye and Dr. Borowsky. In our meeting of April 23, 1968 (with memo) we told Mr. Avergun, Dr. McDermott, and Dr. Sikowski that the supplement was not acceptable for the following reasons:

1. It was based on only one *in vitro* study.
2. Incorporation of these data into the labeling would give a false implication of clinical efficacy.
3. Tetracyclines are not drugs of choice in the treatment of staphylococcal infections.
4. As voluntarily stated by Dr. Sikowski, this represents a transient phenomenon. Staphylococci develop resistance to new tetracyclines in a short period of time.

Multiple attempts by the representatives to modify the statement were immediately rejected by us. It was decided that Pfizer will submit a rephrased statement for our review and evaluation. Several weeks later we received a communication from Pfizer withdrawing the original supplement.

FDA never encouraged the use of these data in promotional material. In fact, our main objection to the incorporation into the labeling was its potential use in promotional literature if it became part of the approved labeling.

APPENDIX V

DOCUMENTS ON DYNAPEN (DICLOXACILLIN) FROM FDA FILES

CHRONOLOGY OF DYNAPEN (DICLOXACILLIN) CASE

BRISTOL LABORATORIES, SODIUM DICLOXACILLIN MONOHYDRATE (DYNAPEN)

November 10, 1965.—Antibiotic Form 5 for sodium dicloxacillin monohydrate submitted by Bristol. This contains suggested regulation for certification of 125 and 250 mg. capsules and 62.5 and 125 mg/5 ml. oral suspension. Clinical data on 198 clinical cases treated with dicloxacillin are also included.

January 6, 1966.—Letter to Bristol from FDA recommending 1) performance of a reproduction study if the product is to be used in premenopausal women and 2) submission of methods, controls and acceptance limits for potency, moisture, pH, identity, crystallinity and microbial assay.

January 28, 1966.—Memorandum from A. Kirshbaum to Mr. Ogles concerning tests performed by FDA on samples of dicloxacillin. The following tests were performed: 1) Assay of 1 mcg. sensitivity discs, 2) Acute toxicity in mice, 3) Microbiological assay for dicloxacillin using the cylinder plate assay method and *Staphylococcus aureus* as the test organism. Using this method 7 of 9 batches showed no loss of potency in two weeks, 4) Bristol's recommended chemical analysis using the infrared spectrum of the beta-lactam moiety. Since this group is shared by all other penicillins, it is suggested that an oxygen flask combustion method for chlorine content be used in addition to assure the identity and purity of dicloxacillin. It is further recommended that Bristol be asked to supply stability data and a reference standard of the drug.

February 10, 1968.—Telephone conversation between J. Davitt and J. Lamar (FDA) and Dr. C. Woodard (Woodard Research Corporation). Concerning teratology studies to be performed by Dr. Woodard for Bristol, FDA recommended that rabbit pups to be delivered by cesarean section should be examined first

grossly, then autopsied for visceral examination and finally examined for skeletal abnormalities. Furthermore it was recommended that all pups be examined.

February 28, 1966.—Memorandum from A. Kirshbaum to R. Norton containing review of proposed regulations for dicloxacillin. The following recommendations are made: 1) A method for percent dicloxacillin in terms of chlorine content should be submitted. 2) Tests for optical rotation and free acid content are possibly desirable but not absolutely necessary. A method for chlorine content is described in detail.

January 27, 1968.—Amendment by Bristol to the Form 5. This contains a revision of the Finished Product Specification with methods for moisture content and pH. The tolerance limits given are moisture—maximum 1% and pH—range 5.0–7.5.

March 25, 1966.—Submission by Bristol of a status report of clinical investigators of dicloxacillin. A total of 469 case reports had been received from 21 investigators at this point.

June 20, 1966.—Conference between FDA and representatives of the sponsor. The following areas were covered: 1) Reproduction studies. Rabbit, mouse and rat studies had been performed. In rabbits, diarrhea had resulted from the initial dose of dicloxacillin causing difficulty in impregnation. In the mouse study stunting and light weight pups had been obtained. The company agreed to repeat this study. In rats there was a question of whether dicloxacillin had decreased fertility. Sections of testes were to be examined but it was unclear whether the ovaries were still available. 2) Toxicity studies. Previous requests by FDA had been satisfied; it was now requested that, since in the 12 week chronic toxicity study autopsy data had been submitted for only a single animal, the information be supplied for the remaining animals. 3) Labeling. It was recommended that the observation that dicloxacillin interfered with the enteric flora of rabbits and inhibited subsequent impregnation be included in the labeling. This would be discussed at a later conference. Dr. Peltier (Bristol) agreed to add to the labeling, statements to the effect that "where sensitivity tests indicated a given staphylococcus was sensitive to Penicillin G, a change to this drug may be considered", that eosinophilia and "occasional but transient SGOT elevations" are adverse reactions to dicloxacillin and that it is advised that "the drug be administered on an empty stomach."

July 1, 1966.—Submission by Bristol of revised package circular incorporating the changes discussed in the conference of 6/20/66 and advising that the trade name "Hypen" has been chosen for dicloxacillin.

July 12, 1966.—Letter from FDA to Bristol advising that, in order to bring the labeling for dicloxacillin into conformity with that of the other penicillinase-resistant, semisynthetic penicillins, the following sentence should appear in capitals or bold face as the beginning of the "Indications" section: "Hypen is particularly suitable against infections due to staphylococci resistant to Penicillin-G (or phenethicillin)." and that, in addition, the following should appear in the same section; "If it is determined that the infection is not due to a Penicillin G-resistant staphylococcus, a change to Penicillin G or Phenethicillin may be considered."

July 12, 1966.—Drug Control Review Notes (FDA). It is concluded that controls are inadequate and that the sponsor should be notified as follows: 1) The 3-(2,6 dichlorophenyl)-5-methyl-isoxazole carbonyl chloride should have a specific identity test. 2) The Form 5 should be amended to specify that the bulk drug and the finished dosage formulations should conform to the applicable Federal Regulations 3) Extended stability data should be submitted for the bulk drug and for all dosage forms.

July 13, 1966.—Submission by Bristol of new labeling incorporating recommendations made in FDA's letter of 7/12/66 and by telephone. Dr. Peltier (Bristol) adds that "We still feel that . . . such a statement (recommending a switch to another penicillin if the patient's infection is not due to a penicillinase-producing staphylococcus) is not justified by the facts. We will continue to accumulate data and will bring this to your attention as more experience becomes available so that we may review it again."

July 15, 1966.—Letter from Dr. William M. M. Kirby (Professor of Medicine, University of Washington) to Dr. Barzilai (FDA). Dr. Kirby states that he has discussed with Dr. Peltier the labeling for dicloxacillin. He says that "it occurs to me that the time has arrived when it is appropriate to say that these drugs (the semisynthetic, penicillinase resistant penicillins) are effective in staphylococcal, streptococcal, and pneumococcal infections . . . In vitro, these drugs are appreciably more active against streptococci and pneumococci than they

are against staphylococci, and by now large numbers of cases have been accumulated to demonstrate clinical efficacy . . . Actually, the wording (of the labeling recommended by FDA) has been based principally on concern about development of resistance of staphylococci to these penicillins, and there is no evidence that this has occurred . . . I am of course advocating penicillin G or V for clearcut streptococcal and pneumococcal infections, but there are certainly many cases where the diagnosis is not clearcut and one wants to start cloxacillin or dicloxacillin . . ."

July 14, 1966.—Initial Medical Officer's Review. 662 of the 780 cases submitted were found acceptable for review by Dr. O'Neill, the reviewer. In all groups of cases, the failure rate was under 6% except in some 51 cases of pneumococcal infection in which a failure rate of 18% was obtained. The following comments are taken from the conclusions reached by this review. 1) "It was expected from early information that this dichlorinated compound would be irritating to the gastric mucosa. This fear was not born out as seen by the 1.5% figure for gastric complaints." 2) "Superinfection occurred 15 times, an incidence of 1.3%. This contrasts with Louria's statement (reference given) that superinfection may be expected up to 30% of the time with semi-synthetics." 3) "Since the blood levels produced by comparable amounts of cloxacillin are half those of dicloxacillin, the dosage of dicloxacillin may be halved . . . The sponsor recommends 12.5 mg./kg./day for children and this is usually adequate, although one investigator frequently felt he had to go up to 25 and 30 mg./kg./day to obtain results. Doses of 4 to 8 grams a day have and can be used in adults." 4) "Dr. J. Lamar of DTE in private communication June 17, 1966 stated that while he is not entirely satisfied with reproduction studies, in essence they were adequate. Studies have been done in rats which are normal; studies done in mice reveal some stunting effect on offspring; and studies on rabbits have shown such peculiar species toxicity of an ecological nature as to make this species of at least very doubtful value. A decision as to whether this information should go into the labeling will have to be made at a higher level." 5) "In summary, then, I certify that this drug is safe and efficacious when used as directed in the proposed labeling."

A note appended by Dr. H. C. Anderson states "I agree except that I do not believe the recommended dose of 125 mg. for 'minor infections' is a safe one and that the minimum dose should be 250 mg. to allow an adequate therapeutic ratio of dose to MIC" (mean inhibitory concentration).

July 20, 1966.—Telephone conversation between Dr. J. C. O'Neill (FDA) and Dr. H. C. Peltier (Bristol). Dr. Peltier registered his continued objection to the concept that the semi-synthetic penicillins, with activity against penicillinase-producing staphylococci, should be reserved for these organisms primarily." He quoted from Dr. Kirby's letter (see 7/15/66 above). Dr. O'Neill told him that the matter would have to be reserved for Dr. Barzilai's consideration.

July 20, 1966.—Submission by Bristol of a literature survey and analysis entitled "Emergence of Methicillin-Resistant Staphylococci". From this review, the sponsor states the belief that "resistance will not become a problem." This review contains 31 references. The following conclusions are offered by the sponsor:

1. There is no evidence that excessive use of methicillin, oxacillin, or cloxacillin has resulted in the emergence of *Staph. aureus* strains resistant to these antibiotics. A higher incidence of restraint strains has been reported in English hospitals where the use of these antibiotics was restricted than in the United States or Canadian hospitals where they were more widely used.

2. Naturally occurring resistant strains have been isolated from individuals who were not treated with these antibiotics and in hospitals where they had not been used. These strains produce penicillinase and are resistant to several antibiotics in addition to penicillin.

3. The emergence of strains resistant to methicillin and the isoxazole penicillins does not appear likely to occur to the same extent as seen with penicillin G. Large scale studies over a five-year period indicate an incidence of less than 1% resistant strains in England and a lower rate in the United States and Canada.

4. Naturally occurring methicillin-resistant strains consist of a mixed population, with a majority of sensitive organisms and a small minority (1 per 1000 or less) of highly resistant cells. The latter are selected by growth in high concentrations of the antibiotic, but tend to revert back to the original mixed population when grown in antibiotic-free media.

5. Methicillin-resistant strains show variable resistance to the isoxazole penicillins, depending on inoculum size and length of incubation. Dicloxacillin is more effective than oxacillin against a large inoculum and may be useful in treating methicillin-resistant strains.

6. Resistance to dicloxacillin develops *in vitro* in the same step-wise fashion found for methicillin, oxacillin, and cloxacillin. There is no evidence that the use of dicloxacillin *in vivo* would be more likely to result in the emergence of resistant strains.

July 25, 1966.—Submission by FDA to Bristol of draft monographs to provide for certification of sodium dicloxacillin monohydrate and pharmaceutical dosage forms thereof. In the same letter it is recommended that a more specific quality control procedure for establishing the identity of the 3-(2,6-dichloro-phenyl)-5-methyl-4-isoxazole carbonyl chloride be established.

July 29, 1966.—Telephone conversation between Dr. A. E. Smith (FDA) and Dr. H. Peltier (Bristol). Dr. Smith requested that the sponsor make 3 minor changes in the package insert for dicloxacillin.

July 29, 1966.—Submission by Bristol of the revised draft labeling incorporating the changed requested by FDA (telephone conversation of 7/29/66). The trade name for the drug is to be changed to "Dynapen".

August 9, 1966.—Telephone conversation between Dr. P. J. Weiss (FDA) and Dr. H. Frediani (Bristol). Dr. Frediani stated that 100 gm. of a proposed standard for dicloxacillin and the 5A molecular sieve to be used in proposed tests would be shipped to FDA. Analytical data for the standard would also be sent.

August 12, 1966.—Submission by Bristol of a manuscript copy of the layout for a five page announcement advertisement for dicloxacillin. The sponsor points out that this advertisement contains the text of the package circular.

August 12, 1966.—Submission by Bristol of proof copy of labels and cartons for dicloxacillin. The sponsor requests that FDA review this material before he proceeds with final printing.

August 15, 1966.—Response by Bristol to the proposed dicloxacillin monograph. The following suggestions are offered: 1) That the concentration used in the toxicity test be changed from 20 to 16 mg. to put it in accord with the dosage used on oxacillin and cloxacillin. 2) That the solution used for the pH test be prepared to contain 10 mg. instead of 30 mg. per ml. 3) That a more specific assay for organic chlorine content be used. 4) That the oral preparation of dicloxacillin be referred to in the labeling as a suspension and not a solution.

Bristol states in this submission that it is their intention to market a 62.5 mg. capsule of dicloxacillin in addition to the 125 and 250 mg. preparations. The formula, manufacturing instructions, finished product specifications, label, carton, and insert are included.

August 17, 1966.—Letter from FDA to Bristol acknowledging receipt of the proposed dicloxacillin standard, lot #66132. Assay data for the stated potency, the reference used, and the assay data for the infra-red and organic chloride results are requested.

August 15, 1966.—Conference between FDA and Bristol. The major subject discussed was the sponsor's claim that Dynapen is effective at a dosage level of 125 mg. given four times daily. It was pointed out that the Form 5 contains data for only 9 adults with penicillin-resistant staphylococcal infections treated at this dose. The sponsor agreed to review their material from this point of view. In addition, the fact that 13 clinical investigators of dicloxacillin have submitted no cases was brought up and an explanation was promised. It was recommended that the statement in the labeling that larger or more frequent doses may be used for more severe infections be changed to read that they should be used.

August 30, 1966.—FDA review of Bristol's letter of 8/15/66. The following remarks are made. 1) There are no objections to the proposed change in the pH test. 2) Potency should not be corrected. "If bulk material is sold for manufacture in finished products, the potency 'as is' should be considered." 3) The percent chlorine test should be retained with the additional statement the "the free chloride content must not exceed 0.5%". 4) The toxicity dose should be kept at 20 mg. since this was proposed by Ayerst and, in any case, different doses are used for 2 forms of oxacillin.

September 6, 1966.—Submission by Bristol of new package circulars for dicloxacillin incorporating several editorial changes. Also included is Bristol's review of resistant staphylococcal infections treated with the low dose form of dicloxacillin.

September 12, 1966.—Telephone conversation between Dr. H. Peltier (Bristol) and Dr. A. E. Smith (FDA). Dr. Smith recommended that in the dosage section of the proposed package insert the words "of the upper respiratory tract" be placed after "mild to moderate infections" and the phrase "higher and more frequent dosage in more severe infections and in infections due to penicillinase producing staphylococci" be inserted.

September 12, 1966.—Submission by Bristol of package circulars incorporating the changes suggested by Dr. Smith (9/12/66).

September 18, 1966.—Submission by Bristol of 111 case reports of patients treated at a dose of 12.5 mg./kg. or less per day and 14 cases treated at doses of 12.5 mg./kg. to 17 mg./kg./per day. The sponsor claims that all but one patient were bacteriologically cured and offers the following points with reference to use of these doses: 1) The average MIC's for dicloxacillin *in vitro* range from 0.016 to 0.3 mcg./ml. 2) After administration of an oral dose of 125 mg. to an adult, peak serum levels are considerably higher than the highest MIC's of sensitive organisms. 3) Although the drug is considered to be highly bound *in vitro* (by serum proteins) the clinical significance of this binding is not known, particularly in view of the rapid excretion and short half-life of the drug. 4) The cases presented offer clinical and bacteriological evidence that the drug is effective in mild to moderate respiratory infections at the recommended dose. 5) Additionally, the 117 staphylococcal infections treated of which 80 were treated at 12.5 mg./kg. or less per 24 hours (including 46 of the 80 due to penicillinase-producing staphylococci) indicate that the agent is highly effective in these infections as well. However, we will accede to your request to gather more data on the treatment of patients infected with penicillinase-producing staphylococci at the low dose.

October 10, 1966.—Letter from FDA to Bristol concerning experience with the assay procedure for dicloxacillin. The recommended infrared method was found to use up too much of the standard and a modification is proposed.

October 12, 1966.—Conference between FDA and Bristol called to discuss Bristol's revised clinical protocol for evaluation of dicloxacillin 125 mg. tablets in streptococcal infections. Under this protocol, cultures are to be taken before therapy, and 48-72 hours following its termination. FDA advised that the least number of laboratory studies which would be acceptable is a white count, hematocrit and urinalysis in each case and that complete specification of the bacteriological methods used should be provided.

November 25, 1966.—Submission by Bristol of revised labeling for Tegopen (sodium cloxacillin monohydrate). In this, the statement advising that therapy be switched to penicillin G in the event that bacteriological studies show the infecting organism not to be a penicillinase producing staphylococcus is deleted. The reasons given for this change are intended by the sponsor to apply also to dicloxacillin, and are as follows: "1) Clinical data obtained to date demonstrates that cloxacillin is safe and effective when used in the treatment of infections due to Group A streptococci, pneumococci and nonpenicillinase-producing strains of staphylococci. 2) It may be ill-advised to change therapy if a staphylococcus initially moderately sensitive to penicillin has been treated with cloxacillin since such an organism might have become more resistant in the interval before the bacteriology results were obtained. 3) There is no evidence from available data to support the development of resistance by staphylococci to the penicillinase-resistant penicillins. In the period during which methicillin has been commercially available, there has been no increase in the incidence of staphylococcal strains resistant to the drug. When resistance does occur, there is no evidence that it is related to exposure to methicillin. If resistance were to develop through a process of mutation, it would be reasonable to have expected a slow but inexorable increase in the percentage of resistant strains during the last six years, probably with outbreaks of resistant staphylococcal infections in individual hospitals or wards. Since neither of these events has occurred, we submit that this constitutes further evidence to support our position."

December 21, 1966.—Submission by Bristol of pathologist's report on the testes of male rats used in teratology studies on dicloxacillin. This report states that all sections were within normal limits and that the treated and control groups were not distinguishable.

January 6, 1967.—Submission by Bristol explaining that in view of difficulties encountered in previous teratological studies with mice, another study had been performed. This study demonstrates that there was no difference between dicloxacillin and penicillin V with regard to parental or fetal findings. No adverse changes with respect to viability, number of pups born, resorption sites or ab-

normalities at birth were found, and examination of the detailed gross findings of skeletal tissues with respect to number of ribs and sternal bone structure and humerus length failed to reveal any difference between the controls and animals receiving graded doses of these antibiotics administered either orally or subcutaneously. A maximum dose of 600 mg./kg./day was employed.

January 13, 1967.—Submission by Bristol of a marketing report for a number of penicillins. This is submitted as support for Bristol's contentions that the incidence of methicillin-resistant staphylococci has not risen despite widespread use of the semi-synthetics. The general utilization of cloxacillin is shown to be comparable to 1) the total penicillin market and 2) that of Bristol's preparations of penicillin G and V.

February 15, 1967.—Comments by Dr. W. E. Dye (FDA) on Bristol's letter of 11/25/66 concerning labeling changes for Tegopen. Dr. Dye offers these remarks: (1 "Expert academic medical opinion continues to support the present labeling for these drugs and to maintain that penicillin G is the drug of choice for the treatment of infections caused by susceptible strains of Gram positive cocci, and that the penicillinase-resistant penicillins should be largely reserved for the treatment of disease caused by penicillinase producing staphylococci. This advice has been obtained from experienced infectious disease experts with well staffed and equipped laboratories . . . Expert medical opinion does, however, concede that . . . for initial therapy while awaiting the results of laboratory tests when the presence of resistant staphylococci are suspected . . . a penicillinase resistant penicillin is indicated." Opinion is divided on whether or not to switch to penicillin G or V if subsequent cultures revealed the presence of penicillin G susceptible streptococci, pneumococci or staphylococci. It is known that short periods of therapy with penicillinase-resistant penicillins can induce the formation of penicillinase in certain strains of staphylococci. This means that the staphylococcus isolated prior to penicillinase-resistant penicillin therapy might be penicillin G resistant 24 to 48 hours later when the results of the drug susceptibility testing on the initial isolate become available . . . I know of no instance where this phenomenon has been of clinical importance. 2) There is no doubt that the safety and efficacy of Tegopen . . . has been or can be demonstrated in the dosages recommended for the treatment of infections caused by susceptible strains . . . 3) The emergence of strains of staphylococci resistant to penicillinase-resistant penicillins does not, on the basis of several years of experience, appear to be a significant problem in this country or in England . . . The (existence) of these organisms, however, and their cross resistance with other penicillins should be incorporated into the new labeling for these antibiotics. 4) If significant changes are made in the labeling of Tegopen, all other manufacturers of penicillinase-resistant penicillins should be notified simultaneously."

February 16, 1967.—Telephone conversation between Dr. H. C. Anderson (FDA) and Dr. H. C. Peltier (Bristol). Dr. Anderson asked whether Bristol would be willing to combine their clinical data with that obtained by the other two producers of dicloxacillin in order to obtain early approval of the Form 5. Dr. Peltier responded that his lawyers were concerned about the possible anti-trust aspects of this proposal and that, furthermore, Bristol was anxious to have the application approved at the 125 mg. dose, which had not been investigated by the other companies.

March 17, 1967.—Conference between FDA and representatives of Bristol. Dr. Anderson (FDA) informed the sponsor that our review of clinical data for dicloxacillin 125 mg. capsules and oral suspension indicated that the low dose is effective against upper respiratory infections due to Group A streptococci and against mild soft-tissue infections caused by *Staphylococci Aureus*. The sponsor is to submit a draft package insert covering these indications.

March 21, 1967.—Submission by Bristol of revised package circulars for dicloxacillin. Minor changes are incorporated in this revision. Also included are case reports for 18 patients with staphylococcal infections treated with the low dose of dicloxacillin (125 mg. 4 times daily in adults and 12.5 mg./kg/day or less in children). The sponsor states that bacteriological cure was established in 17 or 18 cases.

March 27, 1967.—Submission by Bristol correcting a minor error in the submission of 3/21/67.

March 28, 1967.—Medical Officer's Review of addendum to Form 5 on use of low doses of dicloxacillin in clinical infections. This report is summarized by Dr. Shurin (FDA) as follows:

Cases of staphylococcal infections treated with oral dicloxacillin have been reviewed. Doses of 1 gram daily in divided doses seem to provide adequate therapy for these infections when combined with other appropriate treatment (i.e. surgery). A very low rate of side effects and no serious complications occurred in 148 patients. The evidence available supports the use of low doses (125 mg. q.i.d. of 12.5 mg/kg/day) in mild and localized infections.

The majority of pneumococcal infections reported in the Form 5 were pneumonias. 250 mg. q.i.d. seems to be the lowest adequate dose for this infection. It may be expected that minor and localized pneumococcal infections will respond to lower doses, but few of these were reported and considered acceptable.

The data strongly supports the efficacy of dicloxacillin, 125 mg. q.i.d. or 12.5 mg/kg/day orally, in treating mild to moderate upper respiratory infections due to beta-hemolytic *Streptococcus pyogenes*. Cures were obtained in over 95% of cases and no instance of post-streptococcal complication or adverse reaction occurred.

March 29, 1967.—Initial pharmacology review of Form 5. A summary of this review by Dr. Orthoefer (FDA) follows:

Structurally, dicloxacillin differs from cloxacillin and oxacillin only in the number of chlorine atoms present in the side chain of the 6-APA molecule. It shares many biological properties with these acid stable penicillin, including their relative low toxicity and adequacy of blood levels obtainable by oral administration.

As with other penicillin compounds, rabbits and guinea pigs suffer a high mortality following treatment with relatively small oral doses of the drug. . . . This is usually attributed to an upset of the normal gastrointestinal flora of these animals leading to toxic manifestations and death. The data presented indicated that dicloxacillin and nafcillin produce somewhat more gastrointestinal damage in these species than other penicillins. . . .

The disastrous effects of dicloxacillin on the dams makes interpretation of the rabbit teratology study, in terms of effects on the fetus, extremely difficult. However, no consistent trends were noted in mouse teratology studies and a 2-litter reproduction study in rats yielded no remarkable evidence of adverse effects.

The rat and dog studies revealed no unusual findings. Dosage levels of over 20 times the proposed human dose were administered to these animals for 12 weeks without adverse effects. Other studies in our files (Ayerst) have shown that dogs can tolerate 500 mg. kg for 6 months and 1000 mg/kg for 2 weeks without adverse effects.

The urinary excretion rate of dicloxacillin for man and dog differ significantly. In human studies 40-75% of a given dose was excreted in the urine within 6 hours . . . in the dog less than 2% is excreted . . . within 4 hours. . . . This difference may be explained by percent protein binding or by a greater metabolism of the drug in the dog.

The data submitted thus far indicate that dicloxacillin capsules are acceptable from a safety standpoint providing all precautions pertaining to penicillin are clearly stated in the labeling.

March 30, 1967.—Conference between Bristol and FDA on labeling. Minor revisions were requested by FDA and agreed to by Dr. Peltier. In their summary, Drs. Smith and Anderson (FDA) state that with these changes, labeling is acceptable.

March 31, 1967.—Telephone conversation between FDA and Bristol concerning controls. With Bristol's agreement to use a minimum potency limit of 850 mcg./mg. for the bulk drug and a dose of 20 mg. for the toxicity, Mr. Norton (FDA) states that "all points of controversy have been resolved."

March 31, 1967.—Drug control review notes state that controls are adequate.

March 31, 1967.—Briefing memorandum by Dr. H. C. Anderson (FDA) concerning dicloxacillin. Dr. Anderson cites the medical officer's reviews of 7/14/66 and 3/28/67 as support for the safety and efficacy of dicloxacillin. The results of a poll of specialists conducted by FDA on the question of labeling for dicloxacillin is discussed as follows:

"We polled a number of specialists in the field of infectious disease and they would agree in large part to the old form of labeling. However, it is my feeling that we sampled a very biased group of individuals, almost none of whom would in their academic work see or treat many of the diseases (streptococcal pharyngitis, bronchitis, superficial skin infections) for which these drugs are advocated. I am in complete agreement with (Dr. Peltier's) letter (of 11/25/66) . . . I am therefore recommending that NDA 50-028 be approved for certification and the labeling as submitted be approved also."

March 31, 1967.—Submission by Bristol of revised labeling incorporating several minor revisions.

April 26, 1967.—Addendum to medical officer's review stating that cases submitted by Dr. William Abruzzi were not considered for evaluation.

April 26, 1967.—Telephone conversation between Dr. Anderson (FDA) and Dr. Peltier (Bristol). Dr. Anderson advised that FDA would like the statement "This drug should not be prescribed for neonates because safe conditions for use have not been established", added to the labeling and that indications for the drug should be revised to mention that the drug is specifically effective against penicillin G resistant staphylococci, and that the latest stability data on the capsules should be submitted.

April 26, 1967.—Submission by Bristol of stability data on 12 lots of dicloxacillin.

April 27, 1967.—Conference between FDA and Bristol. It was recommended that certain questionable side-effects such as listlessness and tiredness be removed from the labeling.

April 28, 1967.—Telephone conversation between Dr. David Holvey (Bristol) and Dr. P. Shurin (FDA). Dr. Holvey inquired about certain cases which were cited in FDA's medical review. Dr. Shurin supplied him with the case numbers of these cases.

May 1, 1967.—Submission by Bristol confirming the results of conference of 4/27/67.

May 31, 1967.—Conference on current problems in labeling of dicloxacillin. Bristol reiterated the desire to recommend dicloxacillin for infections due to all sensitive Gram-positive cocci. Their position is as follows: (1) In well controlled studies, Bristol has not been able to demonstrate any disadvantage of dicloxacillin, as compared to penicillin G or V in the treatment of streptococcal pharyngitis.

(2) The early fear that staphylococci would develop widespread resistance to semi-synthetic penicillins has not been borne out by many years' usage. (3) The contested claims are now permitted for such drugs as novobiocin, tetracycline and triacetyloandomycin. Therefore, more stringent requirements for dicloxacillin are discriminatory. (4) It is possible though not borne out by any clinical evidence, that an infecting strain of *Staphylococcus* may increase its level of penicillinase production during the course of an infection. In such a case, switching treatment from dicloxacillin to penicillin G following the results of original cultures, would be contraindicated. (5) It is unwarranted to change treatment when the patient is responding well, if there are no real or theoretical disadvantages associated with the original medication. Dr. Hodges (FDA) agreed to take the matter under further consideration.

June 10, 1967.—Drug control review notes state that "a 12 month expiration period could be approved for all potencies of the capsules and for both potencies of the powder for oral suspensions. The stability data for the reconstituted suspension indicate that it would be stable for 7 days at room temperature and for 14 days on ice."

June 13, 1967.—Submission by Bristol informing FDA that the original oral suspension of dicloxacillin has been found to be so bitter as to be unpalatable. The company has, therefore, developed a method of wax coating the drug and claim to have "determined that the drug in this coated form is as readily available as the original formulation." This amendment contains manufacturing instructions, specifications, test methods, stability data, labeling, blood level studies and samples of this formulation.

June 14, 1967.—Letter from FDA to Bristol recommending that the package insert be revised as follows: 1) The listing of the organisms should include "penicillin G resistant and penicillin-G sensitive staphylococci. 2) There should be a statement to the effect that "if it is determined that the infection is not due to the penicillin G resistant staphylococcus, a change to penicillin G or phenethicillin may be considered . . ."

June 19, 1967.—Conference called to discuss inclusion of the above statement (item 2, 6/14/67) in the labeling for dicloxacillin. Bristol's position on this has been exhaustively cited above (see notes for 5/31/67, 11/25/66 and 7/20/66). The FDA position remained that widespread use of dicloxacillin and related drugs for various infections due to Gram-positive cocci may lead to their declining usefulness as antistaphylococcal agents and thereby produce a serious public health problem.

June 28, 1967.—Medical Officer's review of data pertaining to the coated form of dicloxacillin for oral suspension. Blood levels and urinary excretion obtained with this preparation were comparable to those obtained with the old formula.

July 25, 1967.—Interoffice memorandum (FDA) concerning test results with the new formulation of dicloxacillin for oral suspension. No difficulties are cited.

July 6, 1967.—Submission by Bristol. In the conference of 6/19/67, it had been agreed by Bristol and FDA to cooperate in preparing a poll of experts on the labeling of dicloxacillin. This submission states that since FDA had subsequently, through Dr. Minchew, declined to cooperate in a personal presentation of this poll, Bristol had gone ahead with it. The written responses of 16 physicians tend to support Bristol's position as outlined above.

July 17, 1967.—Interoffice memorandum (FDA) points out that Bristol's poll did not raise question of whether therapy should be switched from dicloxacillin to penicillin G., if warranted by bacteriological results.

July 18, 1967.—Submission by Bristol giving tabulated summary of results of their poll on dicloxacillin. The important questions and responses are as follows:

(1) Is there data to indicate a trend to an increasing number of strains of staphylococci becoming resistant to the semi-synthetic penicillinase-resistant penicillins?

Yes—4, No—10.

(2) In your opinion should a penicillinase-resistant penicillin be reserved for the treatment of infections due to penicillinase-producing staphylococci when the penicillin has been shown to be highly effective both bacteriologically and clinically in infections due to streptococci and pneumococci?

Yes—2, No—12.

(3) In your opinion would reserving a penicillinase-resistant penicillin for infections due to penicillinase-producing staphylococci prevent or materially delay the appearance of resistant strains of the organism?

Yes—0, No—13.

September 1, 1967.—Telephone conversation between Dr. Peltier (Bristol) and Dr. McQueen (FDA) concerning labeling for dicloxacillin. Dr. McQueen stated that the recommendation of the Medical Advisory Board on this question would be ready within a week.

September 7, 1967.—Telephone conversation between Dr. Peltier (Bristol) and Dr. McQueen (FDA). Dr. Peltier was informed of the wording for the indications section of the package insert recommended by the Medical Advisory Board.

September 12, 1967.—Conference convened to discuss Bristol's latest proposed labeling for dicloxacillin in the light of the Medical Advisory Board recommendation. The only point remaining at issue was the statement advising use of penicillin G or phenethicillin in the event that the infecting organism prove not to be a penicillinase producing staphylococcus. Bristol wanted to substitute the phrase "other appropriate antibiotic therapy" for mention of specific drugs. Dr. Hodges (FDA) stated that this substitution seemed to obscure the intent of the advisory board and would not be acceptable. After discussion this statement was agreed to by both parties: "When the infecting organism is susceptible to penicillin G the physician is advised to use penicillin G, phenoxymethyl penicillin, phenethicillin or other appropriate antibiotic therapy, because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semi-synthetic penicillins."

* * * * *

September 21, 1967.—Telephone conversation to Bristol by Dr. Smith (FDA) to request minor revisions in the labeling.

September 25, 1967.—Conference between FDA and Bristol on moisture limits, pH and chlorine content of dry powder for oral suspension. Resolution of these matters was agreed upon.

September 26, 1967.—Submission by Bristol of additional stability data to substantiate their claim of a 12 month expiration date.

September 26, 1967.—Submission by Bristol of confirmation of matters discussed in telephone conversation of 9/21/67.

October 5, 1967.—Pharmacology review of coated form of dicloxacillin oral suspension. There is no expectation of increased toxicity associated with this formulation but it is suggested that data on toxicity of the flavoring agents be requested "as a final precautionary check."

October 9, 1967.—Telephone conversation to clarify questions about flavoring agents in dicloxacillin oral suspension. Bristol is to submit toxicity studies of this formulation in the near future.

October 16, 1967.—Submission from Polak's Frutal Works, Inc. Middletown, New York, supplying information on the composition of Imitation Antibiotic Flav-O Lok 3X 610049.

October 17, 1967.—Submission from Fritzsche Brothers, Inc. New York, N.Y. containing the formula for Aromalok Pineapple Imitation # 31194.

October 19, 1967.—Letter from FDA to Bristol stating that approval of package circulars for dicloxacillin has not been made.

October 23, 1967.—Submission by Bristol containing formulas of flavoring agents used in spray-coated dicloxacillin for oral suspension and acute toxicity data in rats and dogs on this product.

October 30, 1967.—Pharmacology review stating that the material contained in the submission of 10/23/67 satisfies the requests raised in the previous review of 10/5/67.

November 16, 1967.—Interoffice telephone conversation in which it is stated that Dr. Wright (FDA) approves of minor change in the wording of the dicloxacillin monograph.

November 16, 1967.—Telephone conversation between Bristol and FDA in which FDA states a preference for retention of the analytical tests originally proposed in the monograph. This was accepted by Bristol.

November 17, 1967.—Drug control review notes stating that stability data are now adequate to support the sponsor's requests, that the flavoring agents are acceptable and that an inspection has indicated that good manufacturing practices are being followed.

December 1, 1967.—Medical Officer's review of additional clinical studies designed to compare the efficacy of two dosage schedules—250 mg qid and 125 mg. qid in the treatment of minor infections due to coagulase positive staphylococci. The following conclusion is offered: "Bristol's contention that dicloxacillin at a dose level of 125 mg qid provides adequate therapy for staphylococcal infections of the skin and soft tissues of moderate severity, is probably justified. I feel that higher doses should be recommended in those cases where there is significant expectation of complications arising from the infection.

January 5, 1967.—Telephone conversation between Dr. Smith (FDA) and Dr. Holvey (Bristol) in which the sponsor was informed of certain further suggested revisions in the labeling.

February 23, 1968.—Conference between Bristol and FDA in which Bristol again presented its position on methicillin resistant staphylococci (see notes of 5/31/67.) 11/25/66 and 7/20/66). Additional data was presented in which it was demonstrated that among Bristol's employees, exposure to semi-synthetic penicillins was not associated with any nasal carriage of methicillin resistant staphylococci, but that a high level of exposure caused carriage of *S. aureus* to be changed to carriage of *S. Epidermidis*. Dr. Minchew (FDA) stated that the other two producers of dicloxacillin had now submitted labeling conforming to all our requests and that these would be acted upon. Similar labeling has been prepared by Bristol but not yet submitted.

February 23, 1968.—Telephone conversation between Dr. Smith (FDA) and Dr. Peltier (Bristol). Dr. Peltier stated that revised labeling would be submitted but said also that Bristol might consider withdrawing its application.

February 26, 1968.—Submission by Bristol of revised labeling for dicloxacillin. The sponsor wishes "to state for the record that we are not in agreement with" the changes requested by FDA and now accepted. The statement noted in the above note of 9/19/67 is deleted.

February 19, 1968.—Submission by Bristol of preliminary results of an in-plant survey of nasal flora. These results are noted in the above note of 2/23/68.

March 5, 1968.—Telephone conversation between Dr. Smith (FDA) and Dr. Peltier (Bristol) confirming wording changes suggested by Dr. Smith for the labeling submitted on 2/26/68. Dr. Peltier agreed that previously submitted promotional material is no longer to be considered.

March 5, 1968.—Submission by Bristol of corrected package inserts for dicloxacillin.

March 5, 1968.—Submission by Bristol confirming the telephone conversation of the same date, and clarifying points raised by a letter of 1/13/67 (these points are clear in the above note for that date).

March 8, 1968.—Interoffice memorandum from Dr. Smith (FDA) to Dr. Ley (FDA) confirming the opinion of the Division of Anti-infective Drugs that the applications of all three companies for sodium dicloxacillin should be approved, and that the labeling submitted by all of them is acceptable.

PAUL A. SHURIN, M.D.

FOOD AND DRUG ADMINISTRATION, BUREAU OF MEDICINE

12TH MEETING MEDICAL ADVISORY BOARD

August 31 and September 1, 1967, Crystal Plaza Office Center, Arlington, Va.

Members of the Board present: Dr. Mark W. Allam, Dr. Harry F. Dowling, Dr. William M. M. Kirby, Dr. John G. Morrison, Dr. Arthur P. Richardson, Dr. Wesley W. Spink, Dr. Norman Kretchmer (September 1 only).

Member of the Board absent: Dr. William R. Mann.

Executive Secretary: Dr. Jean D. Lockhart.

PROCEEDINGS

Dr. Minchew welcomed the Board and announced that Dr. Ley was at the American Society of Pharmacology and Experimental Therapeutics meeting being held at Howard University on the same day.

Dr. Paul Shurin presented the first agenda item: dicloxacillin. After discussing the general pharmacology of this semi-synthetic penicillin he pointed out that in the past, labeling for such agents included a statement advising the physician to switch to penicillin G if culture showed the infecting organisms to be sensitive to it. However, the three companies producing dicloxacillin are resisting the inclusion of such a switch statement in the labeling of these drugs, all of which are ready for new drug approval in other respects. Questionnaires sent both by FDA and by the pharmaceutical firms to antibiotic experts have not resolved the issue.

Dr. Hodges pointed out that if Bureau policy is changed on dicloxacillin it should also be changed for methicillin, nafcillin and oxacillin. As things stand now manufacturers of the latter three drugs may not promote their drugs as the drugs of choice for routine use against susceptible gram-positive cocci.

Dr. Minchew indicated the concern of the Bureau of Medicine, that the semi-synthetic penicillins will be used for routine practice and that in the next few years resistance to these organisms will develop. Already seven strains of staphylococcus at Boston City Hospital have been shown to develop complete cross-resistance.

Dr. McCleery explained the implications of the labeling as they apply in advertising.

Dr. Kirby doubted that there was a sound rational basis for placing these restrictions on the labeling of semi-synthetic penicillins. During the past seven years, there is little or no evidence of any resistance developing. Dr. Dowling agreed with Dr. Kirby that the evidence is slight, but was impressed with the strains found at Boston City. Dr. McCleery expressed the wish that the switch statement be strengthened rather than deleted.

Dr. Dowling expressed reluctance to label a drug advising the physician to use one or another drug, since this comes close to deciding relative efficacy, something the Congress did not wish the FDA to do at the time of the 1962 amendments.

Dr. Morrison pointed out that the care of many patients especially the aged is conducted not in hospitals but in nursing homes or in other sites where no culture facilities are available. Several Board members expressed concern at the physician's choice being restricted.

Dr. Morrison moved that the labeling for dicloxacillin contain 3 general statements; 1) "When the infecting organism is susceptible to penicillin G the physician is advised to use penicillin G, V, or phenethicillin, because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semi-synthetic penicillins." 2) "The principle indication is in treating infections due to penicillinase producing staphylococci or in initiating therapy when there is the possibility of a resistant staphylococcal infection." 3) "This product is also effective in treating streptococci, pneumococci, and penicillin-sensitive staphylococci."

Dr. Dowling seconded the motion. Those in favor were Drs. Allam, Dowling, Morrison and Spink. Those opposed were Drs. Kirby and Richardson.

Following lunch the Board reconvened and Dr. Charles N. Rice, Chief, Toxicology Information Program, National Library of Medicine, described his program and its relationship to the recommendations of the President's Science Advisory Committee on the handling of toxicological information as well as to the FDA handling of toxicologic data. The program headed by Dr. Rice aims to develop a user-oriented system which will supply information services and

product. It is also planned to develop a directory. Dr. Rice noted that the FDA is a source of valuable data on toxicology and has made strides in making this information available, FDA will logically be a prime contributor and client of the bank at the TIP.

Dr. Rice's plan includes: (1) The establishment of a registry of sources of information, (2) The establishment of a center for the dissemination of literature including technical reports, working papers, etc., and (3) The establishment of a program for critical evaluation of literature.

Dr. Allan B. Lisook spoke next on prison facilities for clinical investigation. He raised questions about what constitutes adequate records, how closely an investigator should be associated with the study and with other investigators, and how carefully should the progress of the investigation be monitored. In tracing the history of investigations which have been questionable he pointed out that in 1962 the work of one investigator was found to be fraudulent and he was eventually convicted for submitting false data to the Government. At present, an investigator's exemption can be revoked by the FDA if his work is determined to be questionable. The Bureau of Medicine is especially interested in the Phase I investigations being performed in prisons. Dr. Lisook noted that the investigational set-up at the McAlester Penitentiary under the University of Oklahoma may be considered a model for good drug investigational procedures.

Dr. Minchew pointed out that FDA guidelines have been developed for the handling of possibly falsified data so that an investigator is brought in for discussion and has several opportunities to explain his manner of conducting drug studies before the Commissioner might take action to withdraw his exemption.

Dr. Kirby noted that the FDA's high standards have upgraded research and Dr. Richardson wondered if ultimately some sort of certification of investigators will develop.

Dr. Wentz stated that industry has trouble getting good studies done. Reference was made by Dr. Minchew to the recent publication of a synopsis of the New Drug Regulations, copies of which had been distributed to the Board members.

Dr. David B. Leof next reviewed the 1967 first phase training program for the new Scientific Associates. In his estimation the course provided a good introduction to the work at FDA. He urged an ongoing professional education program in the Bureau of Medicine. Dr. Ethridge of George Washington University, who was present during this presentation, concurred. Dr. Minchew felt that the Bureau will have to have some type of course annually. Dr. Richardson commented that such a course would be a good opportunity for Fellows in clinical pharmacology as well.

Mr. Julius Hauser, of the Office of the Associate Commissioner for Compliance, next reported on the comments received from the public on the proposed new advertising regulations. Twenty-three such comments had been received to date, prominently lengthy comments from the PMA and the Pharmaceutical Advertising Club of New York. The PMA comments consist of a 27 page letter discussing the regulations in detail and a 46 page legal brief. Mr. Hauser quoted from some of the comments and noted that of them all those of the PMA were the most intelligent and constructive. He indicated, however, that a hearing would likely be necessary on the subject. Dr. Dowling suggested that the opinion of the Board members as to the answers received be solicited again either by mail or at the next meeting of the Advisory Board. There seemed to be general concurrence.

In answer to a question, Mr. Hauser stated that he did not think the advertising regulations would result in a decrease in advertising since the pharmaceutical firms need to promote their own brand name product.

On the second day of the Advisory Board meeting, Dr. Ley presided as Chairman.

Dr. Ley opened the discussion by soliciting comments on a proposed "Dear Doctor" letter on sulfonamides which had been distributed to the Board members on the close of the previous day's meeting. The FDA purposes to send this letter to all physicians. Essentially, the letter points out that sulfonamides, while recognized as effective in the *prophylaxis* of streptococcal infections, have not been shown to be effective in the *treatment* of streptococcal infections so as to prevent subsequent occurrence of Rheumatic Fever. The Board members requested some discussion of the papers on which the conclusions presented in the letter had been based. Dr. Ley pointed out that these papers had been reviewed both by FDA staff and by the American Heart Association. Several of

the studies were cited and quoted. The general problem of communicating with the physician was discussed, as there seemed to be disagreement concerning the effectiveness of "Dear Doctor" letters.

Dr. Ley noted that a periodical to physicians has been suggested and is under consideration. Dr. Dowling urged more signed articles in Journals such as the *JAMA* or the *New England Journal of Medicine*.

Dr. Richardson also supported some form of regular communication.

The "Dear Doctor" letter itself was not discussed further except for Dr. Spink's comment that penicillin itself does not prevent the development of rheumatic fever, as implied in the letter.

The next three speakers discussed the desirability of uniform labeling.

Dr. Edwin Ortiz first described the steps leading up to the uniform labeling of oral contraceptives. The most recent revision of oral contraceptive labeling was in June 1967. Several meetings have been held with the oral contraceptives manufacturers concerning labeling and also one concerning the manner in which effectiveness may be expressed.

Dr. Alan Smith described problems with uniform labeling for tetracyclines. The FDA proposes two package inserts; one for pediatric dosage (liquid), and the other for adults (tablet/capsule dosage forms). The manufacturers of tetracyclines, however, vigorously resist generic labeling and oppose the concept of uniform labeling. They raise various objections, including differences of opinion about the age for the tooth staining warning. Dr. Kirby, who is on the NAS efficacy review committee which is considering tetracyclines, pointed out that physicians are *disease* oriented, not *bacteria* oriented and recommended the phrase "Diseased, due to ——— organisms" rather than a list of organisms, in the labeling of tetracyclines. Dr. Alan Smith noted that Lederle's Acromycin lists 50 different diseases. Drs. Spink and Morrison concurred that diseases should be listed. Dr. Dowling pointed out that the tooth warning would not be needed in parenteral products and Dr. Kirby agreed.

It appeared to be the consensus of the Board that pediatric and adult labeling inserts should be different, and that one should accompany the liquid and the other the tablet/capsule preparations.

(Dr. Morrison left the meeting)

Dr. Ley noted that on about August 1, the need for developing a recommended format for the package insert was discussed. The Bureau felt that it would be better to develop a set of *guidelines* for package inserts. This would later be useful for a compendium. A Bureau of Medicine committee has deliberated and has set down a tentative suggested outline of labeling guidelines.

Dr. Jennings continued the discussion of the labeling guidelines, reminding the Board that at their previous meeting some of these questions had been described: the wording of pediatric dosages, pregnancy warnings, and the need for detailed pharmacology discussion and bibliographic references. He supported the concept of uniform labeling in that it would convey information and provide education as well as avoid promotional aspects. Dr. Jennings also distributed an example of a package insert (Indocin) as well as revision suggestions for the same drug insert. "The package insert is our principle product," said Dr. Jennings.

Dr. Dowling suggested that under the Adverse Reactions heading a distinction be made between reactions *definitely* established and those *not definitely* established, as was done with the oral contraceptives. He also noted that a long list of reactions to drugs loses its effect, if it is so lengthy.

Dr. Jennings favored a package insert in two parts, the first part having simple directions for use and the second part containing a fuller explanation.

Dr. Ralph Smith noted that there are two different types of uniform labeling: (1) for related drugs (like oral contraceptives, phenothiazides and phenothiazines) and (2) for the same drug put out by a number of firms. The latter is a simpler problem, some of the panels at the National Academy of Science are talking about developing model package inserts for drugs of the latter type. Dr. Smith noted that the format for a package insert is already pretty much standard and has been fairly well accepted by the firms without need for any regulation. Both Dr. Smith and Dr. Ley pointed out that the guidelines for labeling were still in a draft form and did not represent established policy. Dr. Ley solicited the comments of the Board members in the next several weeks, both on the guidelines and on the "Abbreviated" package insert which Dr. Jennings had written for Indocin.

Following lunch Dr. Arthur Wentz discussed the Conference on Experimental Design which was held on August 24 and 25, at the FDA. The drug category considered was anti-convulsive drugs. Five workshops were held on the first day and each included representatives from industry, FDA and from the academic world. The purpose of the conference was to exchange ideas on the problems of good experimental designs.

Each workshop had been given a series of questions for their consideration and on the second day there was open discussion of the workshop findings. Dr. Wentz read some of the conclusions of the workshops and agreed to send the summary of the conference proceedings to the Board members.

Dr. Ley discussed the labeling of fatty foods. A few months ago the AMA Committee on Nutrition recommended; 1) In foods containing over 10% fat the manufacturer will be allowed to label the fat content by quantity. (example: 50% polyunsaturated fat) 2) This labeling would be voluntary. The FDA is having to review these recommendations carefully and revise its agency position. The Bureau of Medicine has recommended to the Commissioner that no medical claims be permitted on the labeling or in the advertising. The new proposal would however, enable the physician to identify foods with certain fat contents, for the guidance of his patients.

(Dr. Morrison returned to the meeting)

Dr. Ley described the recruiting program planned by FDA to replace the Public Health Service officers who will be leaving in July of '68 and of '69. He noted that Dr. Goddard is interested in developing an active training program here.

After a coffee break Dr. Ley commented on several problems facing the Bureau including the backlog of supplements, the labeling guidelines, the Modell criticisms, the creation of many new Bureau of Medicine Advisory Committees, and the continuous problem of how to communicate with the practicing physicians.

Dr. Kretchmer invited the Board to meet at Stanford in December and the dates of December 14 and 15 were chosen before the meeting adjourned.

I certify that I attended the twelfth meeting of the Food and Drug Administration Medical Advisory Board on August 31 and September 1, 1967 and that these minutes accurately reflect what transpired.

JEAN D. LOCKHART, M.D.,
Executive Secretary.

MARCH 26, 1968.

Director, Bureau of Medicine

Acting Director, Division of Medical Advertising/OMS

Labeling for Dicloxacillin products

Bristol Labs, Syracuse, N.Y. (AF 15-068) "Dynapen," NDA 50-028

Wyeth Labs, Philadelphia, Pa. (AF 13-548), "Pathocil," NDA 50-011 NDA 50-092

Ayerst Labs, New York, N.Y. (AF 19-003), "Veracillin," NDA 50-046

The proposed package inserts, as revised, for the subject products have been reviewed as requested. The major differences between the 3 labels appear to have been resolved. However, several differences still exist which may deserve consideration before final approval.

I. Dr. Minchew, in his addendum at the end of our memo of December 5, 1967, expressed concern over the open-ended dosage recommendations in the "Veracillin" labeling. In reviewing this, it became apparent that now *all three* package inserts have open ended dosage instructions. Also, the "Veracillin" dosage instructions, in addition to being open ended, recommend a dosage for both adults and children with severe infections twice that of the other two products, i.e. 500 mg v.s. 250 mg and 50 mg/Kg/day v.s. 25 mg/Kg/day respectively.

II. Wyeth's labeling for "Pathocil"

A. The disclaimer statement leading into the "Adverse Reactions" section has not been omitted. Not only is this type of language absent from the other two package inserts, but it is the type of statement which lends itself to misuse and abuse in promotional material, and in our opinion, has no rightful place in official labeling.

B. "Indications section—In reference to page 1:

1. Present paragraph 4 should be moved to follow present paragraph 1.
2. Present paragraph 3 should be moved to follow present paragraph 5 so that it will immediately precede the paragraph beginning "Indicated surgical procedures..."

C. "Adverse Reactions" section—The statement dealing with changes in liver function studies is still vague and non-specific. The other two package inserts specify that these consisted of elevations in SGOT and alterations in cephalin flocculation.

D. "Dosage and Administration" section—The statement that dicloxacillin is best absorbed when taken on an empty stomach (1 to 2 hours before meals) is still absent, although it is present in the other two package inserts. In his memo of January 15, 1968 Dr. Hodges stated that this point had not yet been resolved, but would be the same in all three inserts. If this point does have some merit, we would suggest it be included in all three package inserts.

III. Bristol's labeling for "Dynapen":

A. In reference to page 2: The second and third sentences of paragraph 1 should be inserted as a separate paragraph following present paragraph 2.

B. The "Actions" section of the package insert for Dynapen capsules omits the word "most" in the sentence "Dynapen is active against [most] Gram-positive cocci . . ." while the package insert for Dynapen suspension includes the word "most." It is recommended these inserts for the same product be consistent.

IV. Ayerst's labeling for "Veracillin":

A. The first page marked January, 1968, job number 66-517, is in the form of an ill-concealed promotion and must be rejected. We suggest that the properties of the drug which follow the "dots" be rewritten in an appropriate discussion form comparable to the "Description" section of the Bristol package insert for Dynapen.

B. In reference to page 2: The present second paragraph of the "Indications" section should be moved below the present fourth paragraph.

C. It was suggested by Dr. Minchew and others during revision of the dicloxacillin labeling that the precautionary statement regarding intestinal overgrowth should read ". . . discontinuation of dicloxacillin therapy should be considered" since in some instances it might not be advisable to discontinue the drug. However, the "Veracillin" labeling states "... medication should be discontinued . . ." It is recommended that the "Veracillin" labeling be made consistent with the other two.

V. It was noted that the labeling for Bristol's and Wyeth's products contain within the "Indications" section the instruction regarding 10-day treatment of Group A Beta-hemolytic streptococcal infections, while Ayerst includes this information in the "Dosage" section. Since dicloxacillin is not ordinarily recommended for treatment of Group A Beta-hemolytic streptococcal infections, it might be considered contradictory to include instructions for treating such infections in the "Indications" section. Because of this consideration it would be appropriate to limit this statement to the "Dosage" section of all the dicloxacillin labels.

Also the words "Group A" should precede "beta-hemolytic" in the Wyeth "Pathocil" labeling.

R. S. McCLEERY, M.D.

MEMORANDUM OF TELEPHONE CONVERSATION

MARCH 27, 1968.

Between: Hubert C. Peltier, M.D., vice president and medical director, Bristol Meyers (AF 15-068); and Herbert L. Ley, Jr., M.D., Director, Bureau of Medicine.

Dr. Ley read to Dr. Peltier the three changes in the approvable letter for the Bristol dicloxacillin product. Dr. Peltier objected mildly but indicated that the changes were consistent with the general philosophical approach the agency was taking to this drug.

Dr. Peltier objected that in his opinion the FDA action on dicloxacillin was discriminatory against this particular product in view of the existing labeling for other products. Dr. Ley pointed out that it would be wise for Dr. Peltier to observe changes in product labeling over the next year. The two individuals engaged in a long discussion regarding the philosophical concept of restriction in usage of the semi-synthetic penicillins. At the conclusion of the discussion neither individual had changed his position and it appeared that Dr. Peltier recognized that from the Commissioner down to the working level the agency was taking the approach of restricting usage by appropriate labeling for the semi-synthetic penicillins.

HERBERT L. LEY, JR., M.D.

U.S. GOVERNMENT MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
April 10, 1968.

To: Director, Bureau of Medicine.

From: W. B. Rankin, Deputy Commissioner.

Mr. Thomas Corcoran, an attorney representing Bristol Laboratories, presented the attached paper to Dr. William H. Stewart, acting for Dr. Philip Lee, on April 9.

Please let us have by close of business April 16, proposed comment from Dr. Goddard to Dr. Lee on this paper.

W. B. RANKIN.

Enclosure: Copy of paper.

The FDA has a theory (hereinafter called the reserve drug theory) that some antibiotics should be limited for use only in the treatment of resistant staphylococci infections even though some antibiotics are also concededly effective for the treatment of infections due to streptococci, pneumococci and non-resistant staphylococci. The FDA has implemented this theory by demanding that the labeling for these antibiotics (which are semi-synthetic penicillinase-resistant penicillins such as oxacillin, nafcillin, cloxacillin and most recently dicloxacillin which is awaiting FDA clearance) state in effect that if laboratory tests determine that the infection is caused by organisms that can be treated by the old line penicillin or by penicillin G, the physician must be advised to stop using the semi-synthetic penicillinase-resistant penicillin.

Curiously enough, the FDA forbids an explanation of this cryptic advice in the labeling. It is understood, however, that it is based on the possibility that some time in the future, there might appear in the environment organisms resistant to semi-synthetic penicillins if they are widely used now. Thus, semi-synthetic penicillins should be reserved for future use by implementing the reserve drug theory through labeling.

However, other antibiotics which have been marketed in the last few years have labeling which omits the elements of the reserve drug theory even though they are indicated also for use in the treatment of infections caused by pneumococci, streptococci and both resistant and non-resistant staphylococci. Such drugs include gentamycin, cephalothin, cephaloridine, methacycline, doxycycline and lincomycin. FDA approval of the omission is peculiar in view of the fact that resistant staphylococci strains have previously appeared shortly after market introduction of similar classes of antibiotics including many of the tetracyclines. Most recently, resistant staphylococci strains have appeared after lincomycin was marketed.

By comparison, although there are rare staphylococci in nature resistant to these penicillins, no significant increase in pathogenic strains which are resistant to the semi-synthetic penicillins have appeared even though methicillin has been in use over eight (8) years and oxacillin for over six (6) years. In contrast, strains resistant to penicillin and penicillin G appeared and increased shortly after those drugs were introduced. This omission, particularly with respect to the labeling for cephalothin and cephaloridine, is indefensible since these drugs are primarily used in hospitals where the problem of resistant infections developing is the most serious.

There are a number of explanations based on experience as to the reasons for the development of strains resistant to some antibiotics and not others. One turns on the distinction between bacteriostatic antibiotics (where resistant strains have usually developed) and bactericidal antibiotics (where resistant strains have not usually developed). It should be noted that such semi-synthetic penicillins as dicloxacillin are bactericidal rather than bacteriostatic, while many of the antibiotics not subject to the reserve drug theory are bacteriostatic.

These random applications of the FDA's policy become even less defensible when it is understood that the failure to apply the theory to the labeling of non-semi-synthetic-penicillin antibiotics would have a patient allergic to penicillin defenseless against some future epidemic of resistant staphylococci infection.

The scientific underpinnings of the reserve drug theory are extremely questionable. But unquestionably, its application has been discriminatory, arbitrary and scientifically unsound. Most recently, by applying the reserve drug theory to dicloxacillin, the FDA is in effect applying the test of relative efficacy in

reverse despite the abundant legislative history that this factor cannot be considered by the FDA in approving new drugs. The FDA has refused to approve labeling allowing the marketing of dicloxacillin for streptococci, pneumococci and sensitive staphylococci because it has been shown to be better than penicillin G and penicillin V in the treatment of bacterial infections in that it is effective against penicillin G-resistant staphylococci.

It is urged, therefore, that the FDA either immediately discard the theory by deleting its elements from the labeling for semi-synthetic penicillinase-resistant penicillins or apply it even-handedly by requiring it in the labeling for all antibiotics which are indicated for use in the treatment of infections caused by pneumococci, streptococci and staphylococci. After that, we hope the FDA should appoint a joint industry-government-academic advisory panel to decide whether the reserve drug theory itself should be finally and uniformly imposed or discarded.

MARCH 28, 1968.

To: William H. Stewart, M.D., Surgeon General, PHS
From: James L. Goddard, M.D., Commissioner of Food and Drugs
Subject: Dicloxacillin as a subject of hearings by the Nelson committee

Reference is made to inquiries directed to you by Mr. Thomas Corcoran, attorney representing Bristol Laboratories, regarding the origin of suggestions that the drug, Dicloxacillin, be considered by the Nelson committee.

In early March the Nelson committee staff contacted the Administration with the request that information be furnished the committee on the investigational drug, MER-29, and on a number of marketed drugs approved post-1962. These requests were handled by the Office of Legislative and Governmental Services of the Food and Drug Administration.

The allegation of Mr. Corcoran that the drug, Dicloxacillin, was suggested for consideration by Dr. Robert McCleery is false; a fact we have verified by interview with Dr. McCleery. The request for information on this drug came from the committee staff.

We recently prepared an information memo for Dr. Lee, dated April 18, 1968, which summarizes the history of Administration position on Dicloxacillin. A copy is attached. This memorandum provides insight into the pressures imposed by drug firms on the Administration in its clearance of new drugs for marketing.

Answering your request for our views about whether you and Dr. Lee should meet with Mr. Corcoran:

There is nothing in FDA's handling of this matter that requires such a meeting. We see no objection to a meeting at which the facts are laid before the attorney. If there is a meeting, the Department should not be apologetic for its position of Dicloxacillin. We have a sound position and should adhere to it.

To: Dr. Philip R. Lee, Assistant Secretary for Health and Scientific Affairs
From: James L. Goddard, M.D., Commissioner of Food and Drugs
Subject: Labeling of semisynthetic penicillins

Recently, Mr. Thomas Corcoran, an attorney representing Bristol Laboratories, questioned the action FDA has taken with regard to a semisynthetic penicillin produced by Bristol.

The attached staff paper gives in considerable detail the FDA position and the manner in which we reached it. I believe we have a sound position and think that we should adhere to it.

Mr. Corcoran is in error when he implies that we are discriminating against his client. You will note from the staff paper that we are taking steps to achieve uniform administration of the statute to the semisynthetic penicillin manufacturers.

MAY 23, 1968.

COMMENTS ON BRISTOL'S "DYNAPEN" LETTER

1. The headline characterization of the drug as a "—High Potency Penicillin— for Skin and Soft Tissue Infections" on envelope and letter is inconsistent with the limited approved indications for the drug. It is indicated, in Skin and Soft Tissue Infections, but only those due to Pen-G resistant staph.

2. The representation that dicloxacillin is "—useful in a *broad range* of skin and soft tissue infections", may be interpreted to mean "broad range" in terms of types of lesions, or "broad range" in terms of etiologic organisms. The latter would be inconsistent with the package labeling.

3. The featuring in the letter of statements such as "low incidence of side effects," "side effects—are exceptionally rare," "lower dosage does mean a lower incidence of side effects," "no direct toxicity," and "a notable lack of side effects" are misleading, especially in the absence of balancing information regarding the facts that, (a) the incidence and severity of adverse reactions are not shown or expected to be less than with other penicillins, (b) super-infection with resistant organisms may occur, (c) safety for pregnancy has not been established, (d) nausea, vomiting, flatulence, loose stools, pruritis, urticaria, skin rashes, allergic symptoms, changes in liver function tests, and eosinophilia have been associated with Dynapen therapy.

4. At no point in the letter, is the need for cultures and sensitivity, and the need to switch therapy if a Pen-G sensitive organism is isolated, expressed.

5. In the 1st paragraph, the indication is given "—in infections of the skin and underlying tissue where resistant staph are *so often* known or suspected." The words "so often" distort the meaning in such a way as to subvert the need to know by cultures or reasonably suspect resistant staph in any specific case.

6. Throughout the letter, in several places where "resistant staph" are mentioned, they are not specified as *Pen G*-resistant staph.

7. In the 2nd paragraph the question of resistance is brought up in a very clever way—"Resistance has not developed *during therapy*." This is misleading in the absence of the information that, however, strains of pathogenic staph resistant to Penase resistant penicillins, including Dynapen do exist and are increasing in numbers and may cause clinical disease and even death.

8. The comparison of blood levels with Pen G and Pen V are objectionable, since Dynapen should not ordinarily be used exchangeably with Pen G or V. It might be appropriate to compare blood levels with oxacillin or cloxacillin.

9. The letter cites clinical data on "a variety of pathogenic staphylococcal infections" including Pen G sensitive staph. Also, overall percent improvement figures are given, I suspect based on clinical impressions and not on follow-up culture data, at least in some cases.

SUMMARY

The ad:

(1) Invites use of the drug in broader indications than those approved.

(2) Does not properly carry out the responsibility to emphasize the need to restrict the use of this drug to infections due to Pen G resistant staph infections.

(3) Does not present a fair and balanced view of the adverse reactions associated with use of this drug.

R. KAUFFMAN.

CORCORAN, FOLEY, YOUNGMAN & ROWE,
Washington, D.C., May 24, 1968.

Dr. JAMES L. GODDARD,
Commissioner, Food and Drug Administration,
Arlington, Va.

DEAR DR. GODDARD: On behalf of our client Bristol Laboratories, this is to express our appreciation to the Commissioner's office for the expeditious handling of the procedures required for the release of Dynapen, the Company's brand of dicloxacillin. While the ambiguities and confusion resulting from the initial handling of the labeling, release, regulation publication and certification of the three brands of dicloxacillin have placed the Company at a competitive disadvantage, the Administration's remedial efforts should permit the Company to make up some of the lost ground.

Unfortunately, new confusion has arisen in connection with certain language contained in the regulation for dicloxacillin which appeared in the Federal Register of May 17, 1968. As you know, antibiotic regulations with respect to labeling normally provide simply that the labeling for a specific antibiotic shall be in accordance with Section 148.3 of the regulations. Section 148.3 in turn is in large measure based on the requirements of Section 1.106 issued under Section 502(f)

of the Federal Food, Drug and Cosmetic Act which requires the language of the label commonly referred to as the Official Package Circular (OPC). The OPC or label for two of the three brands of dicloxacillin are attached hereto. You will note that the 3rd and 4th paragraphs under "Indications" for Bristol Laboratories' brand of dicloxacillin state as follows:

"Clinical studies demonstrate the drug is also effective in the dosages recommended in the treatment of respiratory and skin and soft tissue infections due to streptococci, pneumococci, and non-penicillinase-producing staphylococci. Infections of other sites due to sensitive organisms may also be expected to respond.

"Indicated surgical procedures should be performed."

Section 149(a) (1) of the dicloxacillin regulation contains the usual language which requires the label and labeling to be in accordance with requirements of Section 148.3. However, Section 149(a) (2) and Section 149(a) (3) provide in effect that in addition to the labeling requirements of Section 148.3 that each package should bear on its label or labeling the following statements:

INDICATIONS

"The principal indications for sodium dicloxacillin monohydrate are in the treatment of infections known to be due to penicillinase-producing staphylococci and in initiating treatment of these infections where a penicillinase-producing staphylococcus is suspected.

"Bacteriologic studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, phenoxymethyl penicillin (penicillin V), phenethicillin, or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

"Substantial changes in these indications will not be permitted. Elaboration to indicate results obtained in clinical trials will require approval."

You will note that this Indications Section differs substantially from that of the approved OPC in that it excludes the 3rd and 4th paragraphs of the OPC but includes a new 3rd paragraph.

As we understand it, the FDA interprets Dr. Ley's letter of May 7, 1968 (copy attached) to mean that after the labeling is approved and sample testing completed for release under Section 507(a), dicloxacillin may be prescribed, dispensed, labeled and advertised before an appropriate regulation appears in the *Federal Register*. Therefore, Bristol Laboratories had the same rights and opportunities with respect to dicloxacillin as its competitors but misunderstood the purport of Dr. Ley's letter.

It follows as a logical extension of the FDA's interpretation that batches of dicloxacillin released prior to publication in the *Federal Register* and batches of dicloxacillin certified after publication in the *Federal Register* are subject to identical label, labeling and advertising requirements, since a contrary conclusion would lead to chaos in view of the lead time involved in the preparation of labels, labeling and advertising and would amount to a negation of fundamental considerations of fairness and consistency which are implicit in the administrative process. Further, the first two paragraphs of the Indications Section for Veracillin (a competitive brand of dicloxacillin) differ in some measure from that required in the dicloxacillin regulation. The additional paragraphs in this OPC Indications Section differ from the OPC for Dynapen and are, of course, entirely omitted from the dicloxacillin regulation.

In attempting to reconcile the seeming difference between the language of the OPC and the dicloxacillin regulation, we have reached the following conclusions:

(1) A type-setting inadvertence accounts for the 3rd paragraph contained in the regulation and the language thereof is not required to be stated in the label or labeling for dicloxacillin.

(2) The Company has both the obligation and right to include the 3rd and 4th paragraphs of the Indications Section of the OPC in the labels and labeling for its brand of dicloxacillin.

(3) The language "substantial changes in these indications will not be permitted. Elaboration to indicate the results obtained in clinical trials will require approval" should be interpreted as follows:

(a) The label and labeling for dicloxacillin must substantially reflect the first two paragraphs under "Indications" contained in the dicloxacillin regulation.

(b) The Company may not elaborate on results obtained in clinical trials without FDA approval unless such trials accurately relate to the language contained in the Indications Section of the OPC.

(c) As a corollary, the Company may elaborate on results obtained in clinical trials if such results accurately relate to the language contained in the Indications Section of the OPC.

We have also considered the possibility that the 3rd and 4th paragraphs of the Indications Section of the OPC were inadvertently omitted from the regulations.

Bristol Laboratories is currently in the process of preparing a request for the convening of an advisory scientific panel to determine the validity and scope of the reserve drug theory. This request will contain the reasons for convening the panel, suggested issues to be decided, the make-up of the panel, suggested ground rules to be followed and reasons why the previous panel did not decide the issue in dispute and other pertinent factors.

In view of the controversies and misunderstandings which have surrounded dicloxacillin and other semi-synthetic penicillins, an early and detailed response in connection with all these matters would be appreciated greatly if we are to be in a position properly to advise our clients with respect to the labeling and advertising for its semi-synthetic penicillins.

Very truly yours,

CORCORAN, FOLEY, YOUNGMAN & ROWE.

MEMORANDUM OF CONFERENCE

Bristol Laboratories, Syracuse, N.Y., AF 15-068.
Dynapen, NDA 50-028.

MAY 27, 1968.

Present (Bristol Laboratories): Mr. Morris S. Weeden, president; Mr. Robert B. Simonton, attorney; Hubert C. Peltier, M.D.; Messrs. Corcoran, Foley, Meers and Lane.

Present (Food and Drug Administration): Commissioner Goddard; H. L. Ley, Jr., M.D.; B. H. Minchew, M.D.; R. S. McCleery, M.D.; J. J. Jennings, M.D.; R. E. Kauffman, M.D.; K. H. Potts, M.D.; Mr. W. W. Goodrich; Mr. H. W. Chadduck.

Subject: Initial Dynapen promotion.

This meeting at 9:00 a.m. this date was requested by the Commissioner in his telephone conversation with Mr. Weeden late Friday, May 24, 1968. Parallel with this action, the Commissioner approved cancellation of certification of Dynapen, including all lots initially certified. Also, action was taken to embargo, at the wholesale level, all shipments of Dynapen. Meanwhile, the Secretary had been notified of the action taken and had been given a copy of the promotional letter in question as well as a copy of the complaint sheet.

Dr. Goddard opened the meeting and, using the DMA comments drafted on May 23, 1968, recounted the principal complaints against the "Dear Doctor" promotional letter headed "new high potency penicillin specific for skin and soft tissue infections." He said that the letter violated every principle discussed regarding the indications for use in the labeling of Dynapen and that was the reason why telegraphic action had been taken to cancel certification.

Mr. Weeden said Bristol had discussed the restricted use of Dynapen, and realizing the competition with penicillin-G decided to tell physicians about the site of infections rather than the cause (organism). Bristol selected skin and soft tissue, which, according to Weeden, were associated with "staph" infections. He went on to say that Bristol had not thought of expanding claims beyond the package insert allowances. On questioning, he and his associates said that the promotional letter had gone to the printer on May 15, was mailed out May 17 and that when the letter was written, Bristol did not have Dynapen available for marketing.

Commenting on the foregoing statement, Dr. Ley pointed out that the Dynapen labeling details had been known to Bristol on March 28. Dr. Goddard emphasized that even if Bristol hadn't been aware of the *Federal Register* monograph details, the promotional labeling was basically wrong due to its lack of fair balance, minimization of side effects, etc. He called attention to the Loridine current ad as a good example of advertising. He said it was hard to understand why Bristol's letter had been the way it was after he and his associates had met with

some 24 firms to discuss bad advertising practices. These had been followed by "remedial" letters, the published details of which are well known to the industry.

Expanding on this, Dr. Goddard read excerpts from the Dynapen promotional letter, one being the claim "notable lack of side effects." He said when the firm exercises the option of calling attention to side effects, it incurs the obligation of presenting a balanced view of side effects. In this case, a few of the more serious side effects should have been named.

Mr. Weeden suggested that the package insert with the letter listing side effects should overcome the fair balance problem. But Dr. Goddard said this was not a replacement for balancing "promotional" side effect information in the subject letter. Dr. McCleery said that the limited experience with the drug at lower dosage levels provides no valid basis for the general claim of lower side effects for the drug.

Messrs. Weeden and Simonton and Dr. Peltier joined in commenting on the concept used in the promotion. They said physicians had been consulted and the result was that they promoted for sites rather than organisms—sites associated with "staph" infections. They said they thought the approved indications had not been exceeded.

Dr. McCleery pointed out that some examples of infections recited in the letter are not typically staphylococcus-associated but streptococcus-associated—"impetigo," "cellulitis," "lymphangitis" and "lymphadenitis"—and that some other listed things like "infected skin ulcer," "postoperative infections," "infected wounds, burns and lacerations" could be due to many organisms other than staphylococcus. He referred to the May 1968 issue of the *American Journal of Diseases of Children* in which there was reported a group of 214 patients with impetigo of which 74% was due to Group A streptococcus.

Dr. McCleery emphasized that there is no legal basis within the approved indications for the slogan "specific for skin and soft tissue infections." He indicated that the letter was replete with non sequitur statements, that there were ample opportunities to be clear, but that this was avoided in a well-tailored misleading message. He said the firm even chose to include a dangerous dose recommendation, in that it emphasized a 125 mg dose without stating it was limited for use only for mild-to-moderate (and localized) infections.

An exchange followed between Messrs Simonton and Goodrich in which the latter advised that the letter should have stood on its own, and while the package insert was included, it did not offset the side effect imbalance and, in any event, the letter was inconsistent with the package insert.

Mr. Goodrich then said that when it was learned how much of the drug had been certified (apparently enough for 44,000,000 units), it was apparent that there was a desire to get into the general penicillin market. Mr. Simonton took the opposite position and said an attempt had been made to limit marketing for approved indications.

Dr. Goddard said that the alternate indication seemed to be presenting problems. He said if it became necessary, that the package insert may be revised to delete the second indication, which permits the physician to start the drug without first knowing the identity of the causative organism. He added that the letter did not provide proper guidance and then asked what was the thrust of the journal advertising.

Mr. Weeden said all Dynapen advertising had been stopped but admitted that at least one ad will appear in the Medical World News issue of May 31.

Dr. McCleery reminded the visitors of the continuing disagreement over many months regarding the package insert reference to "strep" and "pneumo," and to the latest FDA move of that paragraph to the end of the indications section. He said that the information was intended not to expand indications but to assist the physician in knowing when it might be safe to prescribe it for the second indication.

The discussion turned to the development of resistance in relation to the letter sentence, "Resistance has not developed during therapy." Dr. McCleery said that the problem of resistance had been handled in a misleading way and called attention to various reports of resistance. When Dr. Peltier stated that "no patient has developed resistance during therapy," Dr. McCleery said this was not true. Dr. Peltier stated that he was not saying there are no resistant strains [which was a reversal of what he had said previously].

Dr. Goddard then said the problem under discussion primarily concerned violation of agreement regarding indications for Dynapen. He requested reports from the visitors as to what the firm is saying to its detail men. He requested

a list of where the ad(s) appeared. He requested copies of telegrams to detail men concerning the present incident.

The discussion turned to remedial considerations. Dr. Goddard said that the first obligation is to correct the bad impressions caused by the promotion.

Mr. Weeden commented about the lack of certified material to market and urged rapid action.

Drs. Goddard and Ley and Mr. Goodrich joined in requesting the following actions. The "remedial" letter should be sent air-mail. A draft will be prepared and sent to Dr. Ley for review. A corrective advertisement will be prepared and run in journals where the defective ad(s) have appeared. Accurate copy of the ads [there are two] will be sent in for detailed review. Corrective information for detailing will be prepared for review.

As to timing, Mr. Weeden said that some material had cleared to the retail level. Mr. Goodrich noted that such material could be subject to seizure. Dr. Goddard requested that Mr. Weeden sponsor the collection of information as to material shipped from wholesalers to retailers. After some discussion, Mr. Weeden said that efforts could be made to have the Bristol field force contact wholesalers. Also, a copy of the telegram will be sent to FDA regarding the embargo of stocks in the hands of wholesalers.

Before leaving the meeting at this point, Dr. Goddard indicated that there was no intention to prolong the embargo unduly but that full corrective action must be taken and that will take time, perhaps 30-60 days.

Dr. Ley continued the meeting and said, in view of the urgency, that a copy of the current ad and of the detail men's brochures should be sent to him for Dr. McCleery's review, which will require time. It was left to the visitors to propose copy for the "remedial" letter, and corrective ad copy if they wished. Dr. Ley said alternatives would be considered if proposed. One possibility suggested by Mr. Goodrich was to convert the remedial ad into a mailing piece.

At this point, Dr. McCleery said that Bristol's competitors had proceeded in an orderly manner and that his group is engaged in assisting them in their promotion; therefore, it would not be fair to postpone existing commitments to handle Bristol's problem exclusively. He said, however, that his review would proceed as rapidly as possible after receipt of the Bristol input.

There was a brief exchange regarding preclearance of promotional labeling of antibiotic drugs. Mr. Simonton seemed unclear as to this but it was emphasized that the regulation revised in February 1968 makes it certain that preclearance is not normally required.

At conclusion of the meeting after Dr. Peltier had summarized the required information to be submitted (copy of current ad, remedial letter draft, and detailing instructions), Dr. McCleery said that if Bristol could get the material to us by Wednesday May 29, we could probably meet Friday to discuss it. He said that, among other things, the material should include a straightforward scientific statement of the place of Dynapen in therapy.

After the meeting, it was arranged that Bristol would meet in Dr. Ley's office at 3:00 p.m., Friday, May 31 to discuss the remedial pieces.

[Note: In lieu of a critique, which because of lack of time could not be prepared in advance of this meeting, there are attached a xerox copy of a marked up copy of the Bristol promotional letter showing areas of error and a copy of a rough draft of comments on the letter dated May 23, 1968].

H. W. CHADDUCK.

BRISTOL LABORATORIES,
DIVISION OF BRISTOL-MYERS CO.,
Syracuse, N.Y., May 27, 1968.

Dr. HERBERT L. LEY, Jr.,
Director, Bureau of Medicine,
Food and Drug Administration,
Arlington, Va.

DEAR DR. LEY: Enclosed is the Dynapen promotional literature as well as the other material you requested from Mr. Weeden:

(1) *Exhibit A*.—Three copies of the enclosed manila index folder and its contents were given to our salesmen to be used as a "keeper." That means the folder was not left with the doctor but rather used as a visual aid by the salesman to help him acquaint the doctor with the new drug. The salesman's instructions were to use the quotation sheet (headed: Antibiotic Resistance

of Staphylococci) to point out the high incidence of resistant staph as a pathogenic organism both in and out of the hospital. The blood level chart was to be used to illustrate the excellent absorption of Dynapen. The balance of the sheets stapled in the folder were to be used to acquaint the doctor with *all* of the other information concerning Dynapen.

(2) *Exhibit B.*—Consists of a copy of a memo from our advertising department indicating those journals in which Dynapen advertising will appear. Tear sheets of each of the ads are also included. You will note, in that memo, the immediate action we took with regard to our advertising following notification from the Commissioner's office on Friday afternoon.

(3) *Exhibit C.*—Is a memorandum from our General Sales Manager outlining the action we took on the distribution front. A copy of the cablegram to our wholesale accounts is attached thereto.

(4) *Exhibit D.*—Finally, enclosed is another memo from our General Sales Manager estimating the amount of Dynapen which has been shipped into retail and hospital channels.

Very truly yours,

WILLIAM D. GULICK,
Vice President, Director of Marketing.

Enclosure: Exhibit A [exhibits B, C, D, omitted].

EXHIBIT A

DYNAPEN SALES APPROACH

Doctor ———, I'd like to talk to you about a new and unique antibiotic that Bristol has just introduced. We're very excited about this product because it's the kind that will fill a real need in your practice and the kind you will find a lot of use for.

It's a new high potency penicillin called Dynapen which is specific for skin and soft tissue infections—the kind you see everyday like abscesses, boils, and infected lacerations, and wounds. You will find even more use for Dynapen now during the summer when the incidence of skin infections increases.

Dynapen is an ideal specific for skin infections especially when you consider that over half of the staph strains isolated from office patients are resistant staph. Because Dynapen is a penicillinase-resistant penicillin, it kills these resistant organisms. Whereas, of course, neither penicillin G or V or erythromycin or tetracycline, for example, work.

Dynapen has undergone more than four years of clinical trials and it's been evaluated in thousands of patients. For example, in 587 staph infections where it was used, 202 were sensitive staph and the cured or improved record was 98%. In 385 cases of penicillin G resistant staph, the cured or improved record was 97%. These are pretty good results, wouldn't you agree?

Now why is Dynapen so effective?

First of all, Dynapen is bactericidal—it kills pathogens outright rather than merely inhibiting their growth. Consequently, resistance has not developed during therapy. On the other hand, therapy with bacteriostatic agents is frequently complicated by the development of resistance. The reason why we call Dynapen a high potency penicillin is its superior absorption. Dynapen is so well absorbed that 125 mg.—the usual dose—produces average blood levels far in excess of the concentration necessary to kill the organism (show blood level chart). This will give you an idea of just how well Dynapen is absorbed at only 125 mg. Peak blood levels are 5 times higher than 250 mg. of penicillin G and 2 to 4 times higher than 250 mg. of penicillin V. The fact is, Dynapen is superior in absorption to all other penicillins.

The 125 mg. dosage has still another advantage. The evidence to date clearly supports the contention that lower dosage means a lower incidence of side effects. In over 1500 patients evaluated for side effects, less than 1% experienced adverse reactions at the usual dose.

Dynapen is a safe drug, Doctor ———. There has been no direct toxicity reported to date—no tooth staining—no blood dyscrasias—no hepatotoxicity—and no photosensitivity. However, as with other penicillins, the possibility of an allergic reaction should be considered.

With all these advantages, you might think Dynapen would be an expensive drug. The fact is the patient cost will be no more than most brands of peni-

cillin—lower than most of the cyclines and mycins—and less expensive than many antibiotics you may now be using to treat skin infections.

What do you think of Dynapen, Doctor ———?

The dosage for Dynapen in skin and soft tissue infections is only 125 mg. q.i.d.—and you can be sure Dynapen will work at this low dosage. For more severe infections such as those you see in the hospital—like post-op infections, infected bed sores, and other traumatic wounds with infections—the dosage is 250 mg. q.i.d. For children, Dynapen is available in an 80 ml. bottle of oral suspension containing 62.5 mg. per teaspoon. The usual children's dose is 12.5 mg./Kg./day in divided doses q.i.d. For example, in a child weighing 44 lbs. the dosage is one teaspoon q.i.d. And, unlike some of the synthetic penicillins, Dynapen really tastes good.

Doctor, I have just given you the facts about Dynapen :

It's the best oral antibacterial you can prescribe for common everyday skin and soft tissue infections.

It's bactericidal.

It produces better blood levels than any other oral penicillin.

It is exceptionally well tolerated.

And, for a change, Doctor, here is a brand new penicillin that's really low in cost.

Doctor ———, I would like you to put Dynapen to the test. For wounds, boils, abscesses, and other common everyday skin and soft tissue infections, will you prescribe Dynapen?

(Make sure you call the Doctor's attention to the fact that details are available in the Basic Prescribing Information Brochure. This is most important with a new product.)

MEMORANDUM OF CONFERENCE

MAY 31, 1968.

Bristol Laboratories, Syracuse, N.Y., AF 15-06S
Dynapen FDA 50-028.

Present (Bristol Laboratories) : Hubert C. Peltier, M.D.; Mr. Robert Simon-ton; Mr. James Meers.

Present (Food and Drug Administration) : H. L. Ley, Jr., M.D.; B. H. Minchew, M.D.; R. S. McCleery, M.D.; R. E. Kauffman, M.D.; Dr. Prince Harrill; Mr. W. W. Goodrich; Mr. L. M. Baukin; Mr. H. W. Chadduck.

Subject: Dynapen.

As planned, and reflected in the record of the meeting of 5/27/68, this conference began at 3:00 p.m., this date.

Prior to this meeting, establishment inspections had been carried out to determine distributions of promotional labeling and merchandise. Approximately 90,000 folders of promotional material for Bristol detail men had been produced; and about 30,000 had been mailed to some 300 such company representatives located west of the Mississippi and in Florida. Except for relatively small quantities of the oral suspension distributed outside the firm's control, about 64000 (x 24's capsules) had been distributed, about 42000 to retail pharmacies and about 3500 units to hospitals. [Figures to be coordinated with Inspector's reports]

Dr. Ley called Mr. Rankin and advised him of the results of inspections and, due to the large amounts of goods released, retail-level recall was recommended for consideration. Mr. Baukin was asked to prepare notification paper for Mr. Rankin's signature.

Three things were settled at this point :

1. Materials was to be recalled to company control.
2. Remedial letter was to be prepared using guideline prepared by Bureau of Medicine.
3. Remedial ad was to be prepared and run in the same journals as the original ad (*Medical Tribune* and *Medical World News*). The ad will consist of correct ad copy, which will also include an appropriate statement showing that this corrective action is required by the FDA.

The visitors joined the FDA group at this point.

Dr. Ley opened the discussion by informing the visitors that the material submitted with Bristol's letters of May 27 and 28, 1968 had been carefully studied on a priority basis. For record purposes, the May 28 letter enclosed a remedial letter draft, a corrected ad mockup, and an example of an envelope with the legend appropriate for transmitting the remedial letter. The May 27 letter enclosed Exhibit A (two manila folders containing promotional material to be

given to salesmen and said to be used as a "keeper"); Exhibit B (copy of memo from Bristol ad department indicating journals in which Dynapen will appear, and ad tear sheets); Exhibit C (a memo from Bristol's General Sales Manager outlining action taken regarding distribution stoppage and copy of telegram to wholesale accounts); and Exhibit D (a memo estimating amount of Dynapen shipped into hospital and retail accounts).

Dr. Ley handed out copies of an FDA-prepared guideline to proper indications for Dynapen, which he proposed as the "core" of the remedial letter. He said the main thrust of the letter should be on these indications, and that other complaints about the initial promotional letter were of lesser importance and therefore not necessary to include.

Mr. Simenton then said he understood that the guideline plus opening and closing paragraphs would comprise the letter. Drs. Ley and McCleery commented that it would be appropriate to use the guideline and to return Monday June 3 with a second draft.

The discussion turned to details in the FDA guideline. Dr. Peltier claimed that the wording relating to "250 mg q. 6h" in the draft was not in accord with the package insert. Dr. Ley indicated that this and other points were open to discussion.

Next, the portion of the guideline dealing with the problem of staphylococcal resistance to the methicillin-family, including Dynapen, was discussed at length. This was led off when Mr. Simonton and Dr. Peltier asked about the scientific basis for the letter's emphasis on the appearance around the world, and recently in the U.S., of resistance to this class of antibiotics.

Dr. Peltier said (as he had said previously) that development of resistance during the therapy of a single patient was a minor problem. But Dr. McCleery interrupted and said it was contrary to reason to mix the two subjects. He agreed that the development of resistance during therapy is a minor problem, but said that the major problem is the increasing frequency of appearance in hospitals resistant strains of organisms of the microbial population in point.

Drs. Ley and Minchew supported this. Dr. Ley said there is good evidence to demonstrate that the widespread use of methicillin has been accompanied by the development of resistant strains. He said this has been the experience with all antibiotics in wide use (hospitals, etc.), but that proof of association beyond reasonable doubt has not been obtained, not even with penicillin G. It was also emphasized that the development of resistance to penicillin G by staphylococci does not occur by a particular strain during treatment of a single patient. However, presumably "genetic-environmental-selection" of penicillin-G resistant staphylococci has led to the prevalence of this problem. It was therefore re-emphasized to Dr. Peltier that the problem of a particular strain of staphylococcus developing resistance during therapy of a given patient is separate from the development and propagation of resistant strains among the microbial population as a whole and should not be equated.

Mr. Simonton said that he wanted Bristol to have the information that FDA had collected.

Dr. McCleery said he would give the references and said the record would show the information was supplied. He gave these references:

1. "The Resistance of Staphylococci to Penicillins and Cephalosporins," a paper by F. H. Kayser, Institute of Medical Microbiology, University of Zurich, Switzerland, given June 26, 1967 at the 5th International Congress of Chemotherapy, Vienna, Austria (6/26-7/1, 1967)
2. "Methicillin-resistant Staphylococci in a General Hospital," E. W. Calley, et. al., *The Lancet*, 13 March 1965.
3. "A screening test for the detection of methicillin-resistant organisms," G. M. Churcher, Department of Pathology, Plymouth General Hospital, Plymouth, England, *J. Clin. Path.* (1968) 21, 213-217.
4. "Resistance to cloxacillin among hospital staphylococci," G. C. Turner and P. E. Cox, Department of Pathology, Sefton General Hospital, Liverpool, England, *J. Clin. Path.* (1967) 870-874.
5. "Antibiotic Susceptibility of Staphylococcus aureus isolated from cases of Bacteraemia in Denmark 1957-66," O. Jessen et. al., an abstract (page 799 of proceedings, B 1-17) of presentation at 5th International Congress on Chemotherapy (see item 1 above).
6. "Combination Therapy of Infections Cause by Methicillin-Resistant Staphylococci with Rifampicin plus Pucidic Acid or Novobiocin," Klaus Jensen, an abstract (pages 783-784 of proceedings, A 1-6/19) of presentation at 5th International Congress of Chemotherapy (see item 1 above).

7. "The History and Development of Oral Penicillins in Japan," Ryoichi Fujii, Tokyo University Hospital, a paper given at the 5th International Congress of Chemotherapy (pages 275-278 of proceedings, C 3/2).

8. "Sensitivity of staphylococcus aureus to lysostaphin, cephalotin, benzyl penicillin and semi-synthetic penicillins," Hawiger, J. and Jeljaazewicz, J., Poland, a presentation (p 35 *et seq.* of proceedings, B 1/8) at 5th International Congress of Chemotherapy.

9. "Studies on enterotoxin-B production in methicillin-resistant aureus-staphylococci," Dornbusch K., Hallander, H. O., Laurell, O., and Lindbom, G., Sweden, an article reporting on cases during 1964-1966 in the University of Uppsala (27 deaths), presented at the 5th International Congress of Chemotherapy (proceedings p 39 *et seq.*, G 1/11).

10. "Changing Patterns of Bacterial Resistance to Antimicrobial Drugs," Gill, F. A. and Hook, E. W., Cornell University Medical College, a paper published in *American Journal of Medicine*, p. 780-795, 39: November 1965.

Other references were mentioned as being available. Later in the meeting Dr. Minchew gave the reference to an article in *Arch. Int. Med.* 111, No. 6, June 1963, titled, "Persistence of Staphylococcus to Methicillin and Oxacillin." He mentioned also that at the annual meeting of 1968 the Epidemic Intelligence Service, National Communicable Disease Center, 22 resistant organisms from 18 patients in one hospital were reported.

In sum, there is ample and continuing evidence that there is cause for concern by the Government and antibiotic producers in relation to the problem.

Dr. McCleery called attention to the Bristol submission in February regarding the resistance problem. He said the information had been discussed within FDA and with outside authorities and found to be invalid for the claims Bristol is making. Dr. Ley concurred and agreed that the Bristol submission was unresponsive to the question of resistance. He reiterated that he felt the FDA-prepared guideline to proper indications should be incorporated into the remedial letter.

The visitors again indicated that the guideline was not in accord with the package insert. The expansion of the contraindications was cited as an example. However, Dr. McCleery pointed out that the same information was in another part of the insert and that it should be emphasized. He said he had hoped that Bristol would be on the "side of the angels" and indicated that on further reflection the firm might come to agree with setting the place of Dynapen in proper perspective, notwithstanding the "legalistic" reliance on the package insert which it was entitled to take advantage of.

On the preceding point, Mr. Meers said in effect that his client is for public health protection assuming that it is reflected in the OPC (package insert).

The discussion turned to the proposed ad. Dr. Ley said the ad copy had been reviewed and found to require a small number of corrections. These were identified by Dr. Kauffman.

There was some discussion regarding the language to be used in identifying the ad as "corrective" (as distinguished from "correct"). This was left for Bristol to consider and to propose language at the next meeting.

Drs. Ley and Minchew emphasized that the Commissioner wanted a "corrective" ad and that it could take more than one form. It was left that Bristol would propose modifications in the submitted ad at the next meeting.

Dr. Ley turned the discussion to considerations of the status of shipment of goods beyond the firm's control. He said the FDA was concerned about the large amount of material so shipped.

Dr. McCleery commented that on May 24 a Bristol detail man had visited an Arlington physician and had left behind the so-called "keeper" promotional material. Dr. Ley indicated that preliminary reports from our inspectors reflected that 90,000 "keepers" had been procured, of which 25,000 were intended for hospitals and 65,000 for physicians.

Mr. Simonton admitted it was intended that the "keepers" be left behind and attempted to reconcile Bristol's (Gulick's) May 27 letter, which said that "3 copies were given to salesmen to use as 'keepers'."

Dr. Minchew said that about 30,000 were shipped on May 23 to some 300 salesmen—(see area covered in first of this memo).

Dr. Minchew asked if the firm had record of what the detailmen are saying now to physicians about Dynapen. (See comment by Bristol later on this question).

The discussion continued to the question of shipments of Dynapen. Dr. Ley said that the figures given in Bristol's letter were not in accord with the inspec-

tor's oral report. (The precise figures are subject to confirmation in the District's RIR).

Dr. Ley said that the Commissioner's office had approved recall of the goods from retail and hospital outlets and that Bristol could expect a communication to that effect.

Dr. Peltier said that recall would be very costly and that if the ad and remedial letter are satisfactory, perhaps recall could be avoided. He indicated that the FDA guideline would not be remarkably difficult to adopt.

Dr. Ley asked how Bristol could freeze the goods in retail stocks. Dr. Peltier admitted that this would be difficult. Continuing on this point, Dr. Peltier said that Bristol would rush out a revised remedial letter draft but that it would take time to implement a freeze order.

Mr. Goodrich said that we hadn't agreed yet as to the ad and that there is no basis for recertification. He added that the freeze order should get out promptly to drug stores.

In answer to Mr. Meers question as to means of expediting appearance of the corrective ad, Dr. McCleery recommended that contacts be made immediately with *Medical World News* and *The Medical Tribune* to reserve space.

The discussion resumed on the content of the remedial letter. Dr. McCleery presented a draft of the FDA version of the opening and closing paragraph. Mr. Meers said that he did not see much difference between the Bristol draft and ours. But Dr. Minchew said the difference between the two versions was that the Bristol letter would mislead physicians as to proper use of the drug, and that it was promotional.

Dr. Minchew asked about the disposition of the promotional pieces in the "keeper" folders. After some discussion of each piece, it was agreed by Dr. Peltier that salesmen would use only the "OPC" for detailing. He agreed to notify District Managers of this limitation.

The discussion resumed on the question of "freeze" and "recall." It was agreed that Bristol would submit for approval a draft of a letter to wholesalers covering letters to all retail accounts. The letters should state the reason for the "freeze." Meanwhile Mr. Rankin was to draft a "freeze" letter to Bristol for Mr. Rankin's signature.

The meeting concluded with minor comments concerning the substance of the remedial letter. [Bristol's revised draft reflects changes which they proposed for consideration.]

The next meeting to discuss continued matters was set for 10:30 a.m. Monday, June 3, 1968, and this meeting ended.

H. W. CHADDUCK.

ROUGH DRAFT OF PROPOSED RESPONSE TO DR. LEE BY DR. GODDARD

SUBJECT: CURRENT POSITION ON LABELING OF DICLOXACILLIN AND OTHER RELATED SEMISYNTHETIC PENICILLINS

I. Background

The Bureau of Medicine believes that the labeling of the semisynthetic penicillins should restrict their primary indications to the treatment of infections due to penicillinase-producing staphylococci or initiating treatment when there is the possibility of a resistant staphylococcal infection. The basis for this position is the view that it is a general public health matter relating to the possibility that penicillinase-producing staphylococci may develop resistance to these antibiotics.

At the present time available data indicate that there is complete cross-resistance of staphylococci among all currently available penicillinase-resistant semisynthetic penicillins. Therefore, the appearance of strains of penicillinase-producing staphylococci resistant to these antibiotics would mean a major setback in the antibiotic armamentarium for drugs effective against these particular bacteria. To date there is but little data to suggest that this problem of resistance is occurring. However, there are reports from Europe, and from at least one hospital in this country that resistant organisms have been isolated. We believe these findings warrant the caution and conservatism we are requesting in the labeling of these drugs at this time.

II. *Expert opinions in resistance*

A. In the process of attempting to resolve the controversy regarding the labeling of dicloxacillin, the FDA, approximately one year ago, drafted and sent a questionnaire to eleven recognized experts in the field of microbiology and antimicrobial therapy. Among those questions asked, two deal directly with the immediate problem:

1. "Do you believe that penicillinase-resistant penicillins are now the drugs of choice for the routine treatment of all infections caused by gram-positive cocci susceptible to their actions?" All eleven experts answered "No."

2. "Assuming you have initiated chemotherapy with a penicillinase-resistant penicillin in a severe infection and the patient is showing excellent clinical response but the cultures now show the causative organism to be a Beta-hemolytic streptococcus or pneumococcus, would you change chemotherapy to penicillin G or V?" Eight answered, "Yes." Two answered, "No." One said, "Probably would not change."

B. Following the FDA poll, Bristol Laboratories drafted a set of questions dealing with the same problem and submitted them to a group of 15 physicians, some of whom are also regarded as experts in the field:

1. Included in Bristol's questionnaire was, "In your opinion should a penicillinase-resistant penicillin be reserved for the treatment of infections due to penicillinase-producing staphylococci when the penicillin has been shown to be highly effective both bacteriologically and clinically in infections due to streptococci and pneumococci?" Eleven answered "No." Two answered "Yes." One felt the question inappropriate, and one did not give a "Yes" or "No" answer.

2. Bristol did not include a question regarding the desirability of changing therapy to Penicillin G or V if culture subsequently showed the organism to be sensitive to Penicillin G or V.

C. On August 31, 1967 the FDA Medical Advisory Board was asked to consider this problem and give their recommendations. The Board was presented with the Bureau of Medicine position and the expert opinions as expressed in answers to all the questions in the FDA and Bristol questionnaires. After considerable discussion, the concern was expressed that the package labeling for these semisynthetic penicillins should limit their indications to thus permit observation whether staphylococcal resistance to these agents does become a significant problem. With this concern in mind the Board voted 4 to 2 to adopt the recommendation: "That the labeling for dicloxacillin contain 3 general statements:

"1. 'When the infecting organism is susceptible to Penicillin G the physician is advised to use penicillin G, V, or phenothicillin, because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.'

"2. 'The principle indication is in treating infections due to penicillinase producing staphylococci or in initiating therapy when there is the possibility of a resistant staphylococcal infection.'

"3. 'This product is also effective in treating infections due to streptococci, pneumococci, and penicillin sensitive staphylococci.'

These recommendations were implemented by the Bureau of Medicine and equally applied in negotiating final labeling for all three dicloxacillin products (Wyeth, Ayerst, Bristol). The approach to labeling for dicloxacillin is well illustrated by the excerpt below:

The principal indication for sodium dicloxacillin monohydrate is in the treatment of infections due to penicillinase-producing staphylococci or in initiating treatment when there is the possibility of a resistant staphylococcal infection. Bacteriologic studies should be performed. When the infecting organism is susceptible to penicillin G, the physician is advised to use penicillin G, V, phenothicillin or other appropriate antibiotic therapy because of the possible appearance in the environment of organisms resistant to the penicillinase-resistant semisynthetic penicillins.

This product is also effective in treating infections caused by streptococci, pneumococci and penicillin-sensitive staphylococci.

III. *Comments on Bristol statement of March 28, 1968*

It is true, as Mr. Corcoran affirms, that the labeling advises the physician to use, or to change to, penicillin G when sensitivity studies indicate the pathogen is susceptible to it. It is not true (see the paragraph #1 above), as

Mr. Corcoran states, that "Curiously enough, the FDA forbids an explanation of this cryptic advice in the labeling."

The FDA did disagree with the desire of Bristol Labs, unique to it amongst the three companies involved, to insert into their package labeling a very extensive and discursive addition to the Medical Advisory Board's opinion. It was believed their additional paragraphs would weaken the labeling's public-spirited appeal to physicians to reserve the use of these drugs to the serious need for which they are so uniquely valuable, and for that reason, the Bureau of Medicine did not accept the Bristol addition.

Data from the National Drug Trade Index (1966) indicates that, in spite of the relatively restrictive labeling of the semisynthetic penicillins, these drugs were being widely prescribed for respiratory diseases, etc. Furthermore, the position of the Bureau has been based on the belief that liberalizing, instead of further restricting, the indications, would be followed by even more open promotion and use of these drugs as routine agents in general office practice for the treatment of common upper and lower respiratory tract infections. This would lead to a much more widespread use than has been the case in the past and could, therefore, contribute to the probability of a more rapid development of strains of staphylococci resistant to these agents. More recently, the Bureau of Medicine has become aware of reports from Switzerland, France, and Denmark of the development of increasing numbers of methicillin-resistant strains of staphylococci.

Because of these facts and concerns, and because of the permissiveness of the labeling for several of these products, e.g., oxacillin and cloxacillin, it is the intent of the Bureau of Medicine to bring the labeling for all the semisynthetic penicillins, and other antibiotics where appropriate, into consistency with its Medical Advisory Board's recommendations, and the approved dicloxacillin labeling.

On March 27, 1968, the Director of the Bureau of Medicine telephoned the Vice President and Medical Director (Dr. Peltier) of Bristol Labs, to explain again the basis for FDA's so-called "restrictive" labeling for dicloxacillin. Dr. Peltier alleged that the labeling was discriminatory against this particular product.

Dr. Ley informed him that this was so only because it was the first reflection of a new policy, and promised him that the labeling of other semisynthetic penicillins, as well as that of other appropriate antimicrobial agents, was already under study for comparable revision.

Dr. Ley ended his telephone memo with this note, ". . . it appeared that Dr. Peltier recognized that from the Commissioner down to the working level the agency was taking the approach of restricting usage by appropriate labeling for the semisynthetic penicillins." It is, therefore, worthy of serious note that on March 28, 1968 Bristol turned from the scientific to the legal-administrative approach, developed the copy of the argument of that date, retained attorney Thomas Corcoran to present this to the Office of the Secretary on April 9, 1968.

Bristol, near the end of its March 28, 1968 position paper, suggests that the FDA apply the so-called "reserve drug therapy" evenhandedly or immediately discard it—this in spite of the assurance, on the day prior, of the Bureau Director that this was underway. Even more improperly, they end their paper with this misleading suggestion: "After that, we hope the FDA should appoint a joint industry-government-academic advisory panel to decide whether the reserve drug theory itself should be finally and uniformly imposed or discarded."

It is misleading because it implies that the FDA reached its position in the absence of relying, in practical fact, on such an "advisory panel," which was known to Bristol not to be the case. It is misleading, also, because it was known to Bristol that the FDA, as part of its decision-making process in reaching the current position, already planned to reconvene the question after an appropriate interval allowed the collection of further evidence as to the potential danger represented by labeling these agents so that they might become in legal fact "Everyday penicillins."

TO BE SENT TO 55,000 RETAILERS AND 480 WHOLESALERS

To : All Wholesalers, Retail Pharmacists, Hospital Accounts
Request for embargo of Dynapen

The Food and Drug Administration has questioned the journal advertising and introductory letter to physicians used by Bristol Laboratories in announcing the marketing of Dynapen (sodium dicloxacillin monohydrate). For this reason the Food and Drug Administration has revoked the release of all lots distributed and has requested that you hold on your shelf all supplies of Dynapen.

Accordingly, until further notice, we request that all supplies of Dynapen be held and not shipped, sold or dispensed.

We will notify you as soon as this material can be released.



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